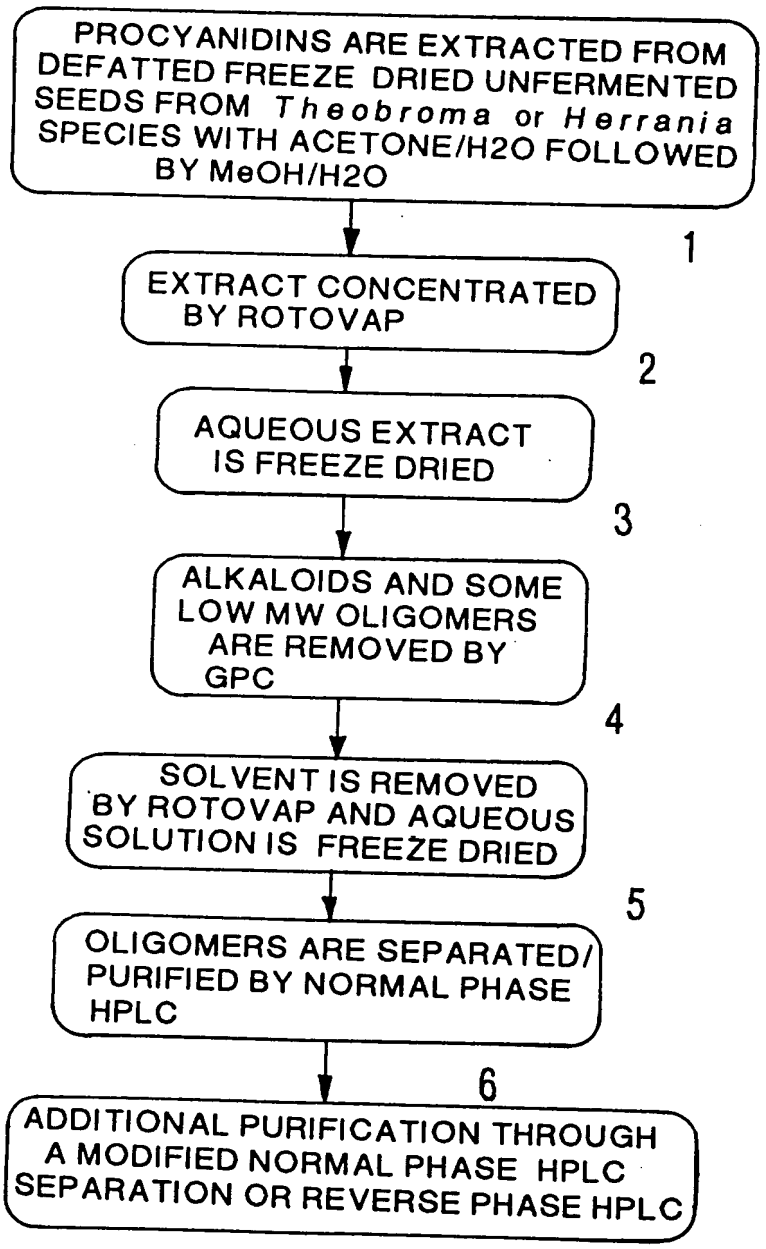
FIG.1

Summary of the current purification protocol



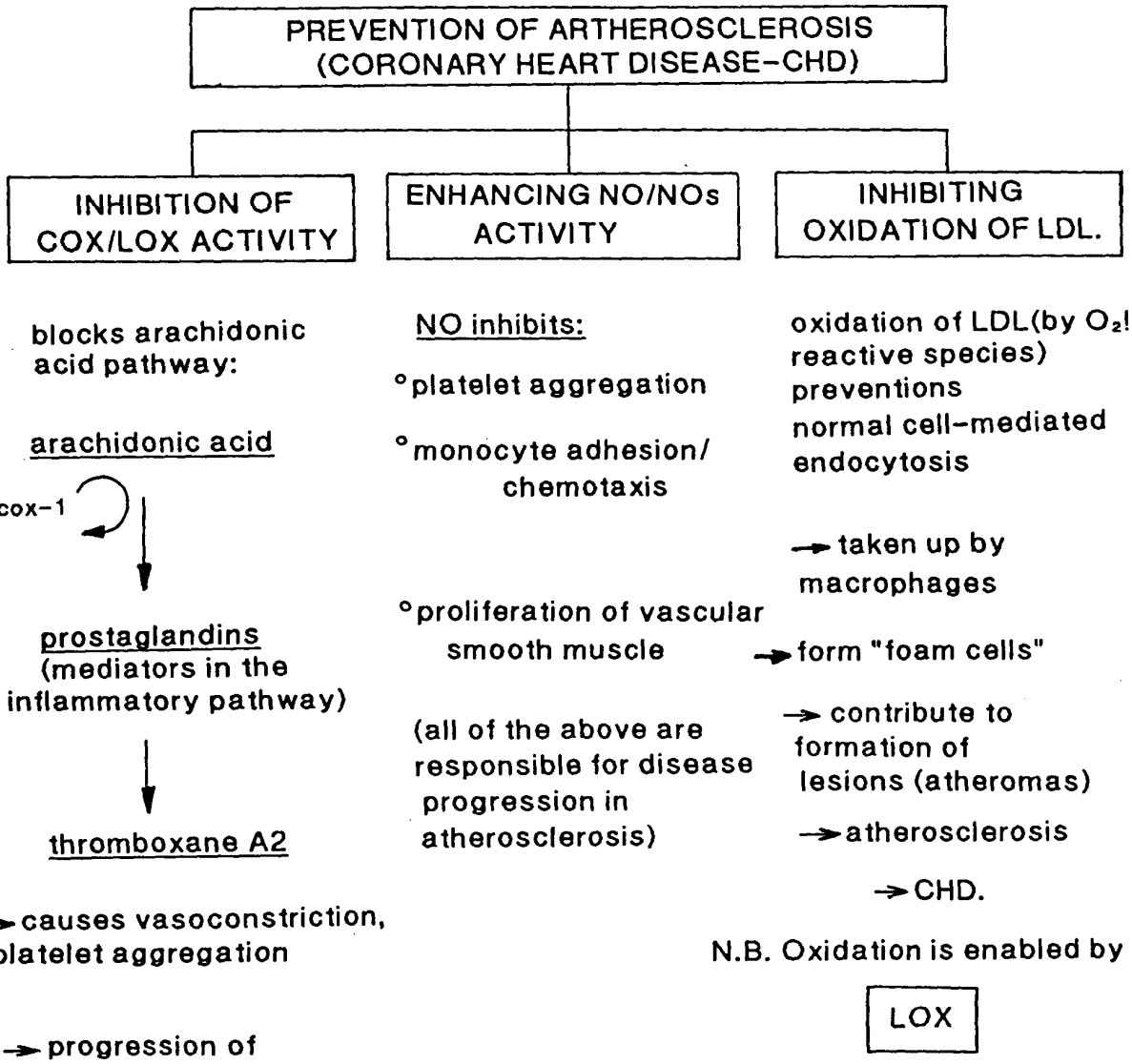
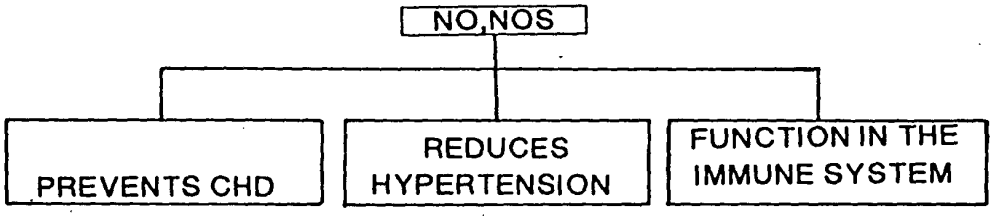


Chart showing the major contributing factors in the progression of Colonary Heart Disease (CHD) and how the activity of cocoa procyanidins contributes to the prevention of the progression of the disease state

FIG.2

The cocoa procvanidins induce the activity of NOS and therefore the resulting production NO, thereby enhancing the health benefits mediated by the activity of nitric oxide (NO).



- inhibits platelet aggregation, monocyte adhesion, chemotaxis and vascular smooth muscle proliferation thereby causing vascular relaxation and preventing the disease progression of CHD.

By lowering blood pressure via the following mechanism:

- vascular endothelial cells release eNOS
- → result in production of NO
- → NO relaxes vascular smooth muscles, increasing vascular lumen diameter
- → lowers blood pressure
- → induces hypotension.

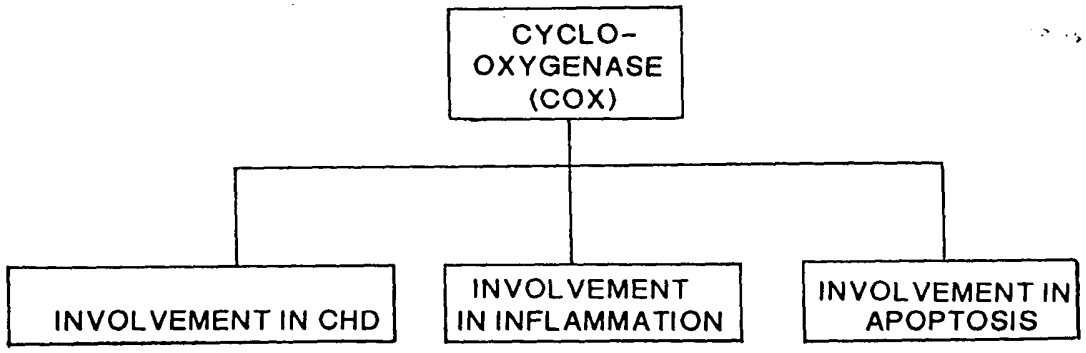
HYPERTENSION RESPONSIBLE FOR CARDIOVASCULAR DISEASES:

including:

stroke
heart attack
heart failure
kidney failure

- Macropages have a different NOS(iNOS)
- iNOS gene transcription is controlled by cytokines
- iNOS activity results in macrophage NO production at sufficient concentrations to inhibit ribonnclease reductase
- → causes inhibition of DNA synthesis
- → potential mechanism of action in anti-tumor and anti-microbial function.

FIG.2b



COX-1 is essential in the arachidonic acid pathway which results in the production of thromboxane.

→ thromboxane and protglandins which promote platelet aggregation and vasoconstriction

→ reulting in progression of atherosclerosis.

COX-1 is an essential enzyme in the inflammatory pathway, the penultimate products of which (the prostglandins) are largely responsible for the inflammatory pathway, the results of which contribute to a variety of diseases including:

→ bowel disease, arthritis, edema, gingivitis/ peridontitis, etc.

COX-2 producing cells lines show enhanced expression of genes known to be involved in apoptosis:

→ potential putative mechanism of killing tumor cells.

The cocoa procyanidins inhibit the production of cyclo-oxygenase, thereby blocking the arachidonic acid pathway, which is responsible for the inflammatory response and the vasoconstrictive and platelet aggregating responses which contribute to the disease progression of CHD.

FIG.2c

FIG.3

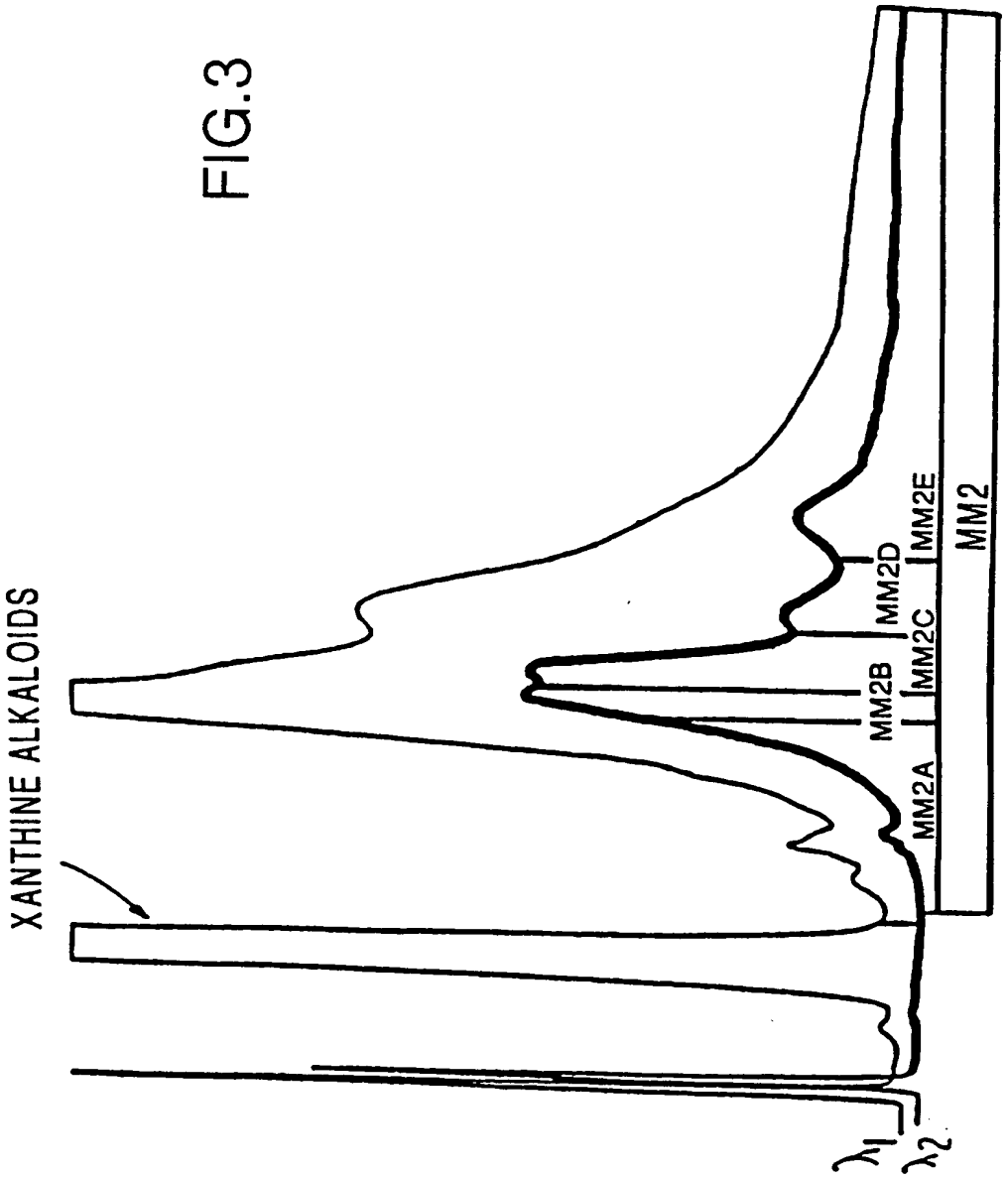


FIG.4

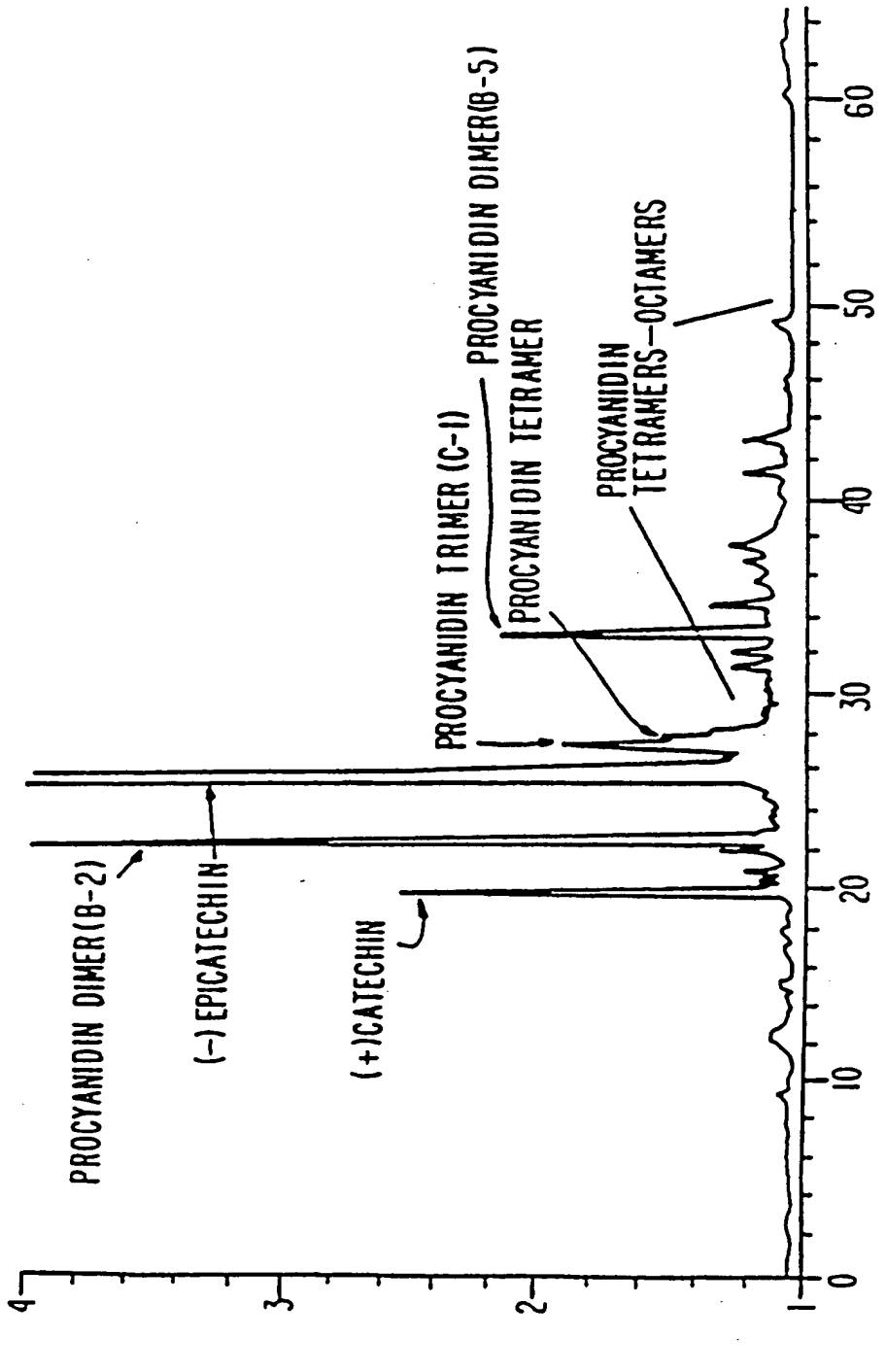


FIG.5

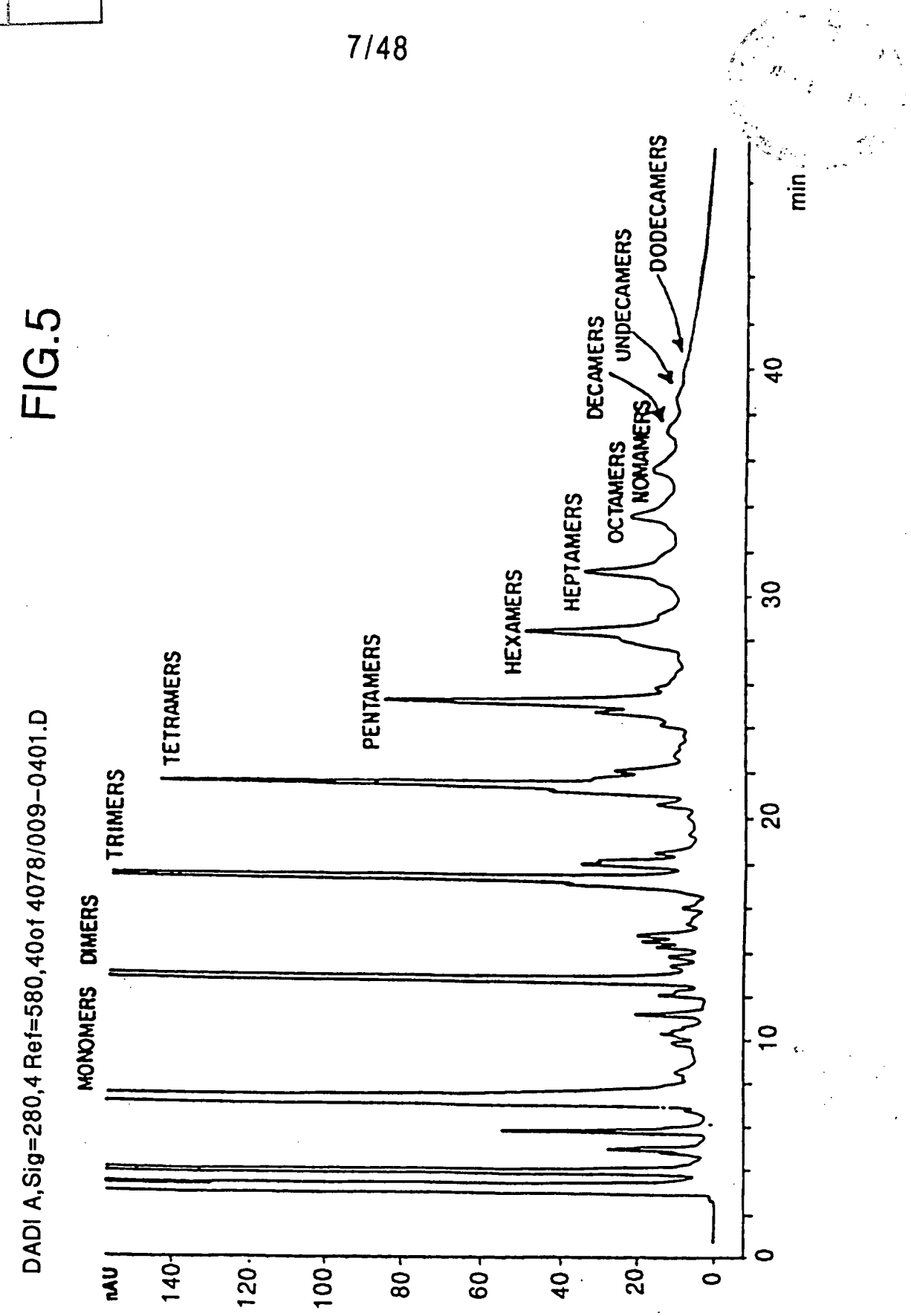


FIG.6

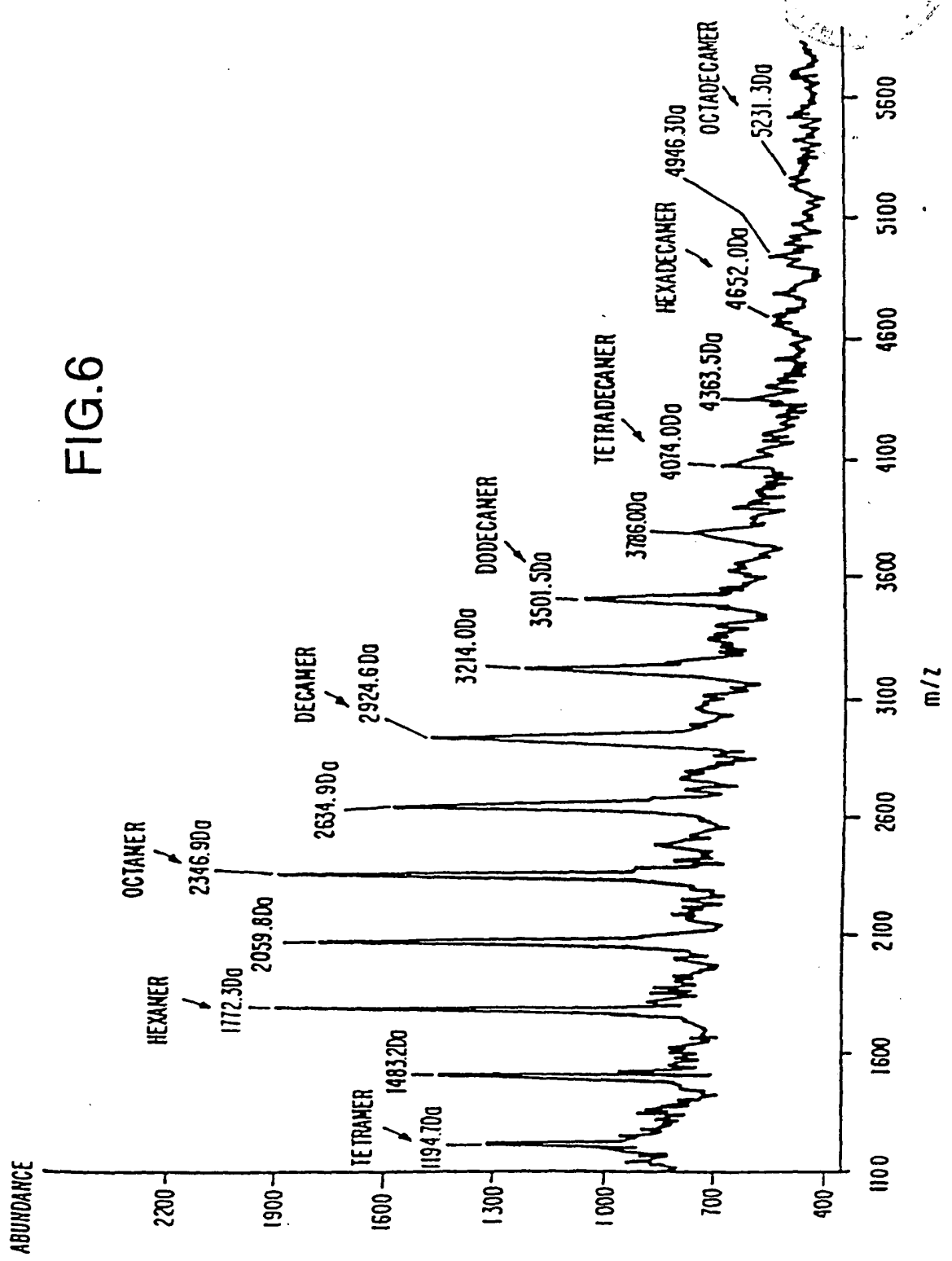


FIG.7

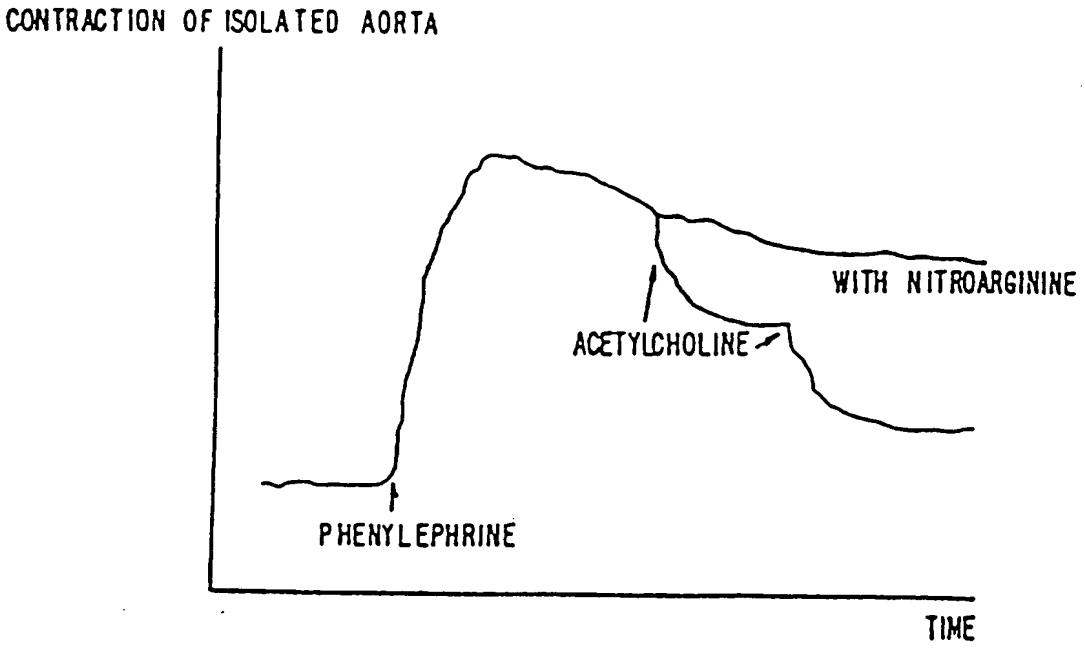
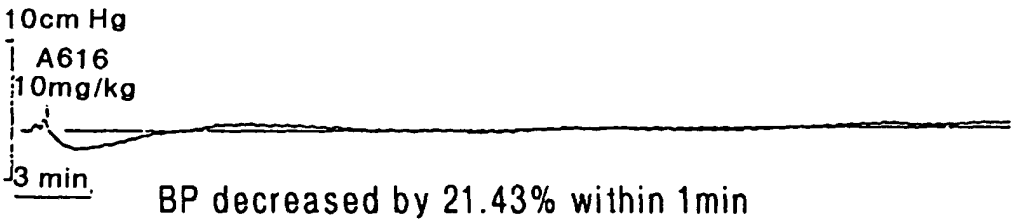


FIG.8A

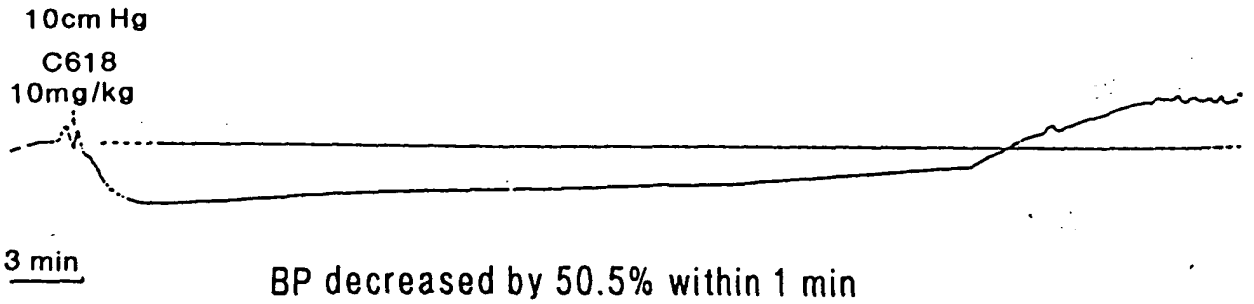
EFFECT OF COCOA PROCYANIDIN FRACTION A ON BLOOD PRESSURE



BP decreased by 21.43% within 1min
BP back to normal value after 1.5 min

FIG.8B

EFFECT OF COCOA PROCYANIDIN FRACTION C ON BLOOD PRESSURE



BP decreased by 50.5% within 1 min
BP back to normal value after 5 min

EFFECT OF COCOA PROCYANIDIN FRACTIONS ON ARTERIAL BLOOD PRESSURE IN ANESTHISIZED GUINEA PIGS

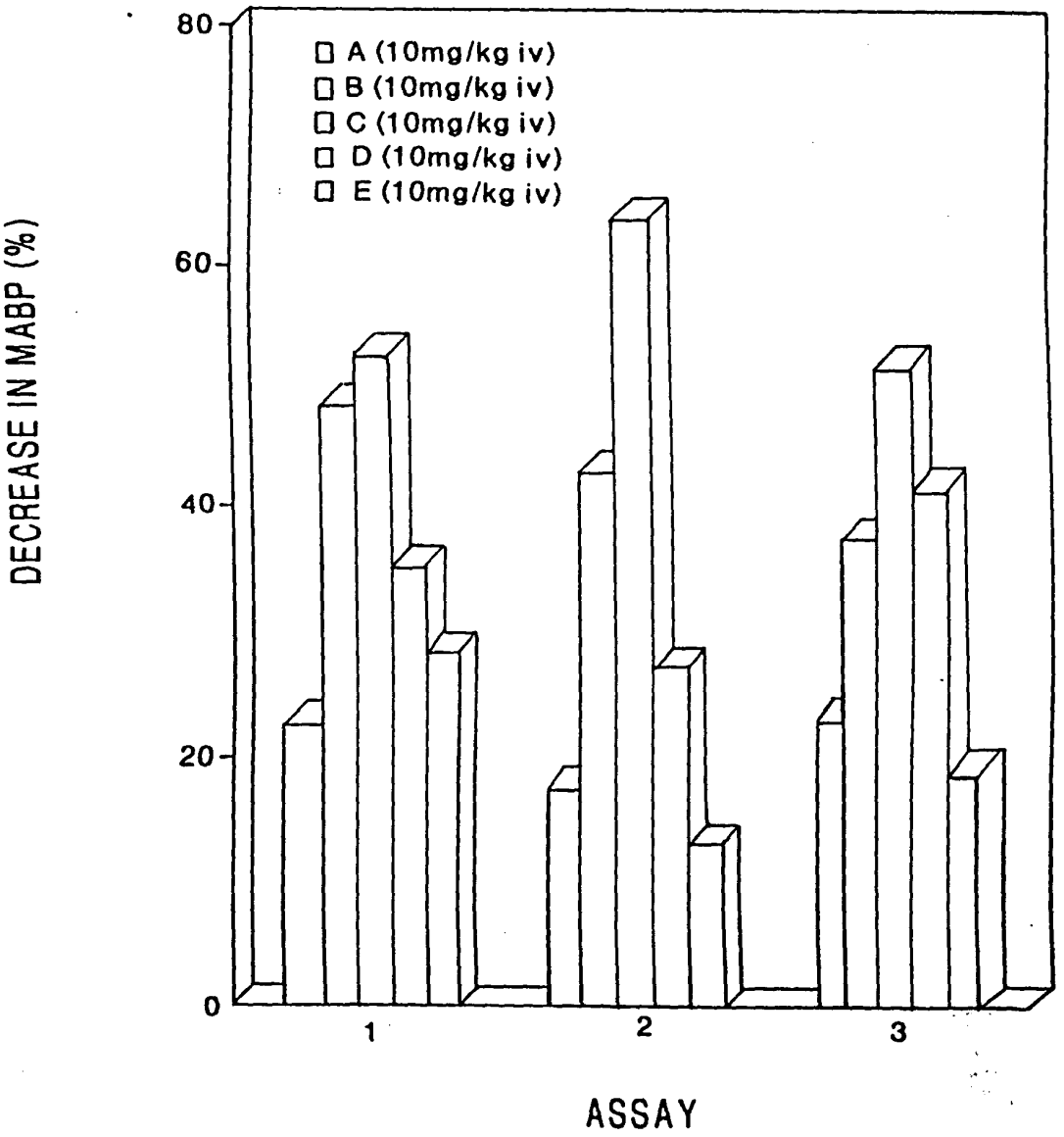


FIG.9

EFFECT OF L-NMMA ON THE ALTERATIONS OF ARTERIAL BLOOD PRESSURE IN ANESTHISIZED GUINEA PIGS INDUCED BY COCOA PROCYANIDIN FRACTION C

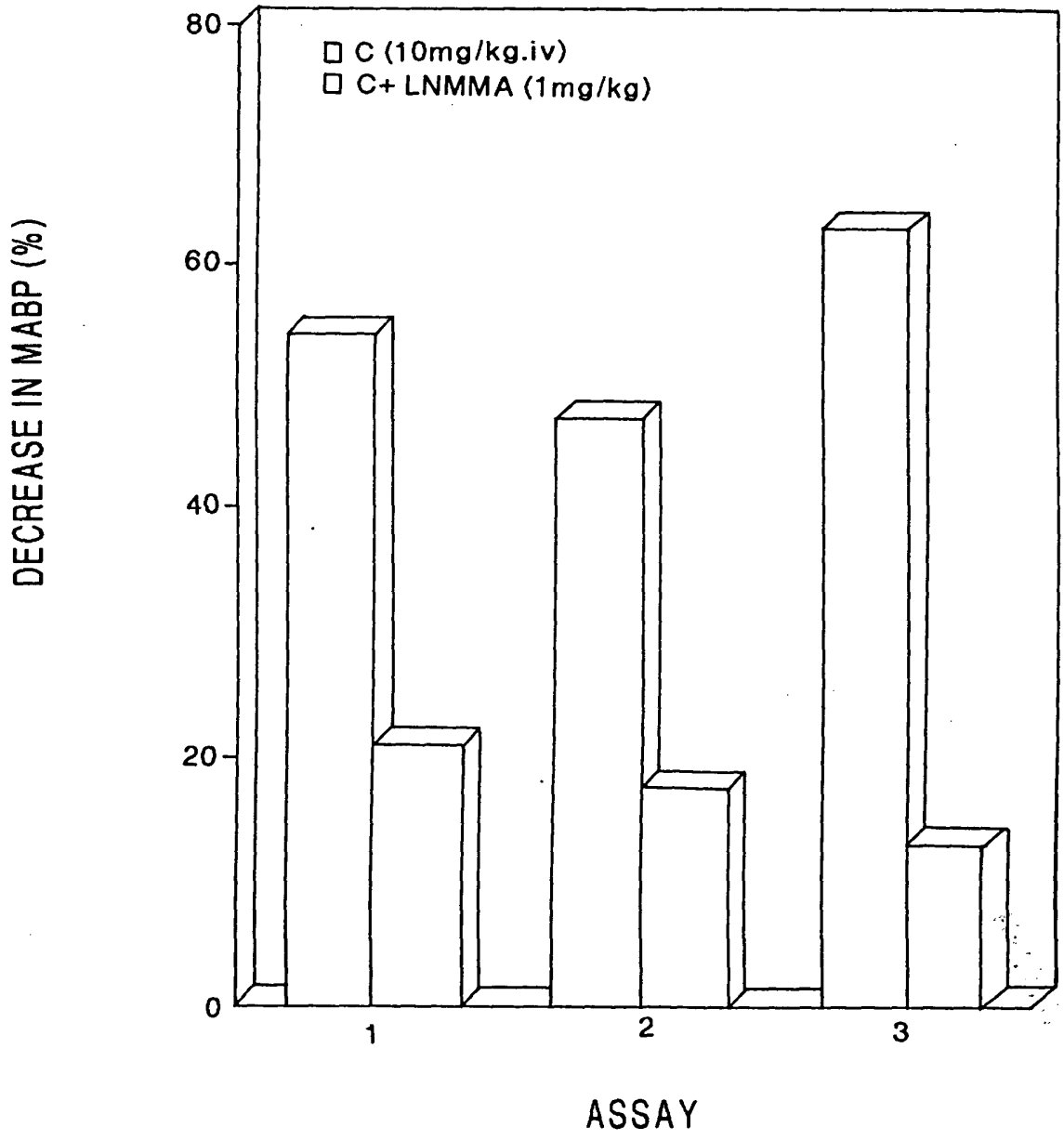


FIG.10

EFFECT OF BRADYKININ ON NO PRODUCTION BY HUVEC

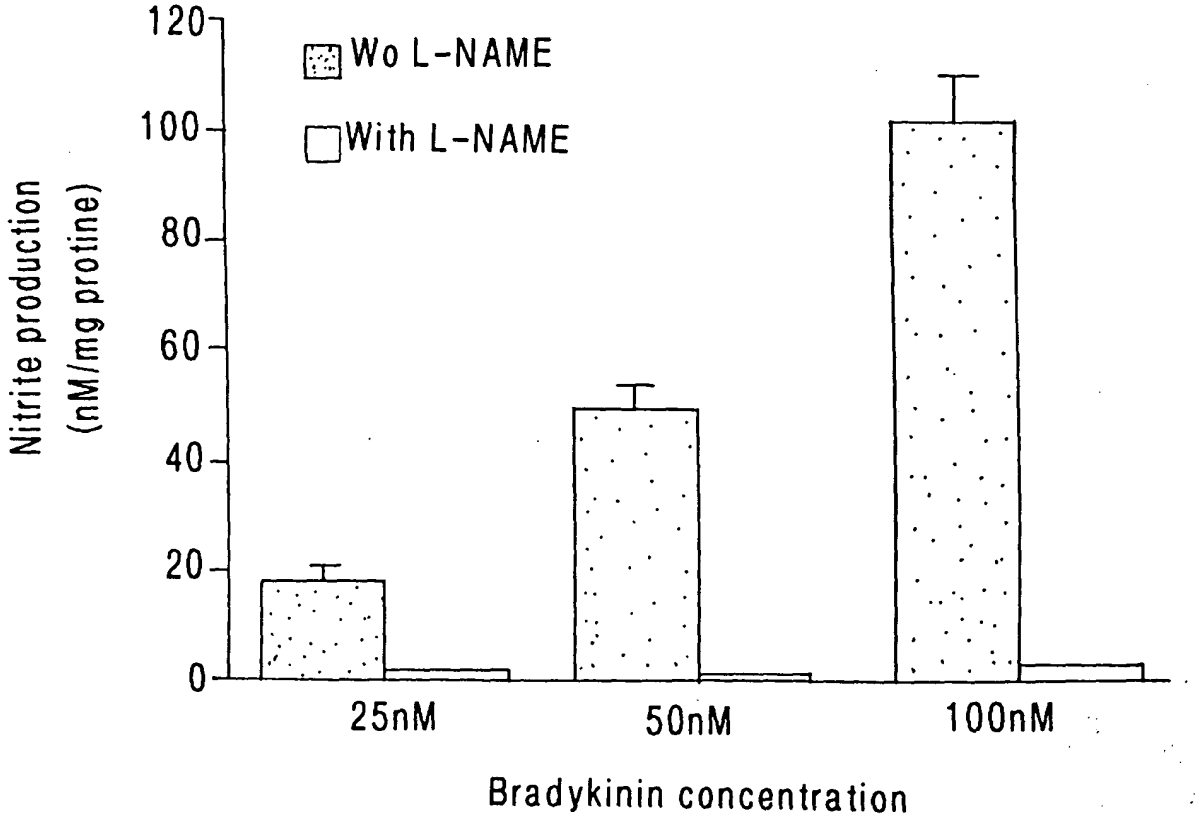


FIG.11

EFFECT OF COCOA PROCYANIDIN FRACTIONS ON NO PRODUCTION BY HUVEC

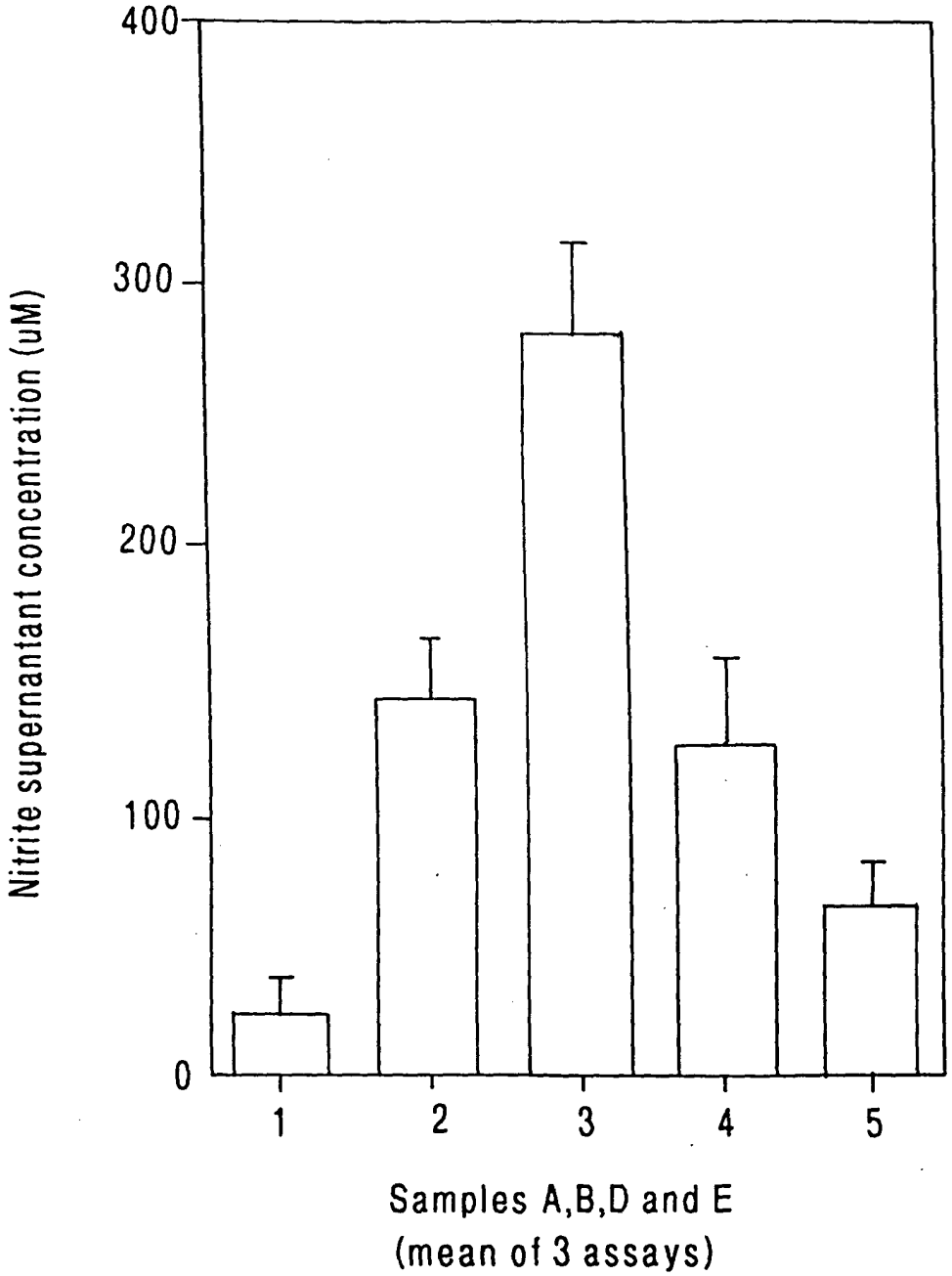


FIG.12

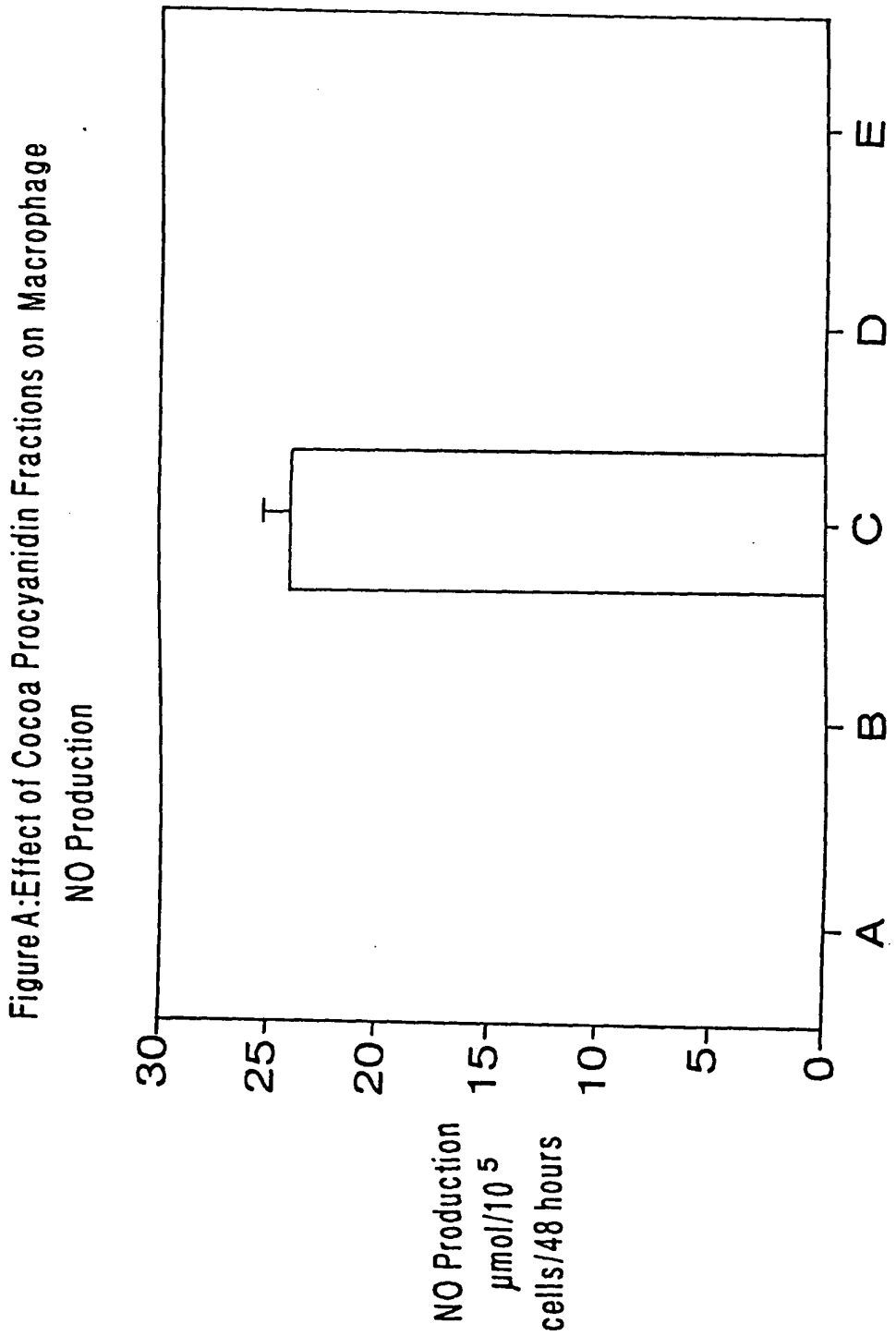


FIG.13

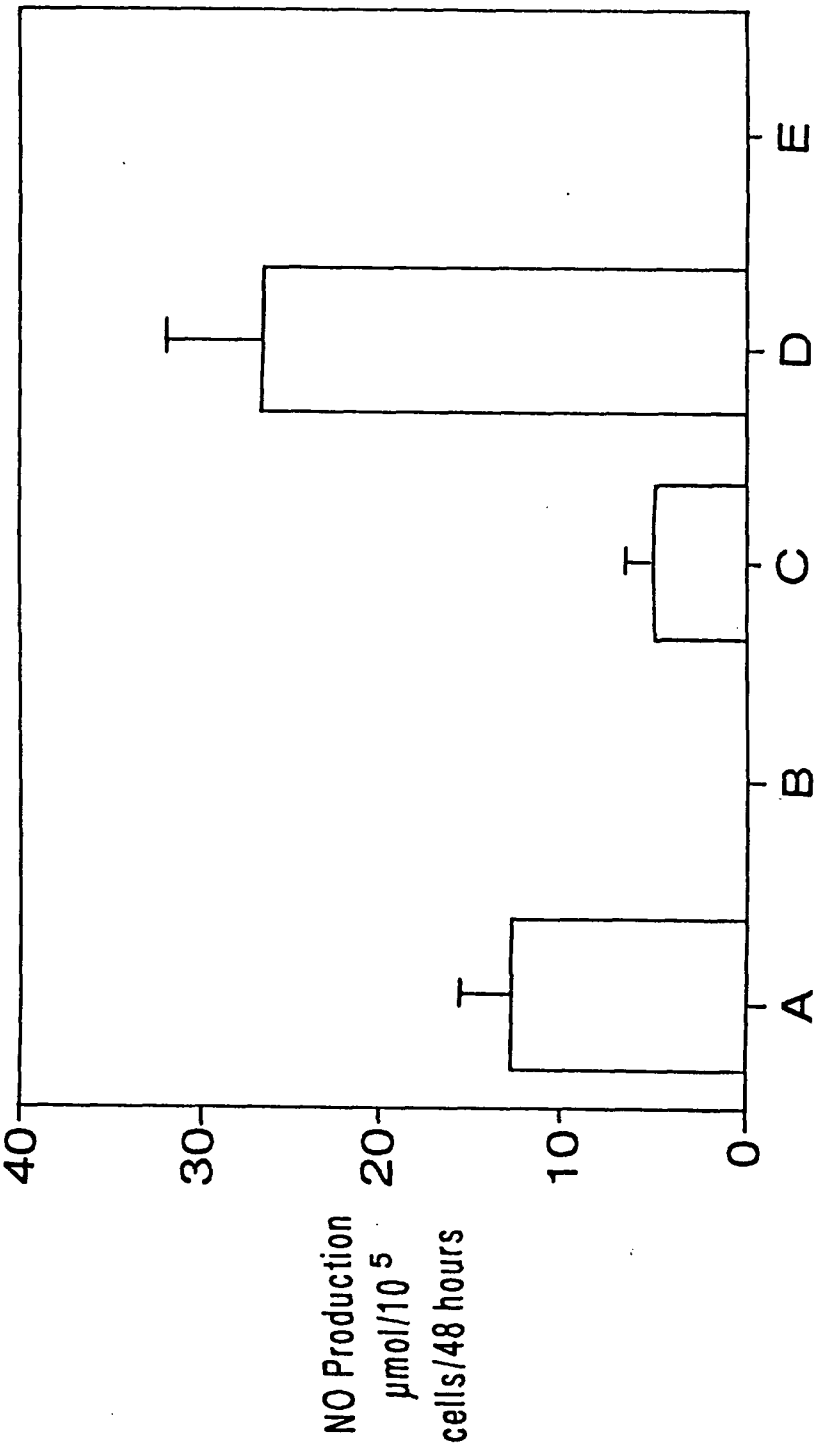


FIG.14

FIG.15A

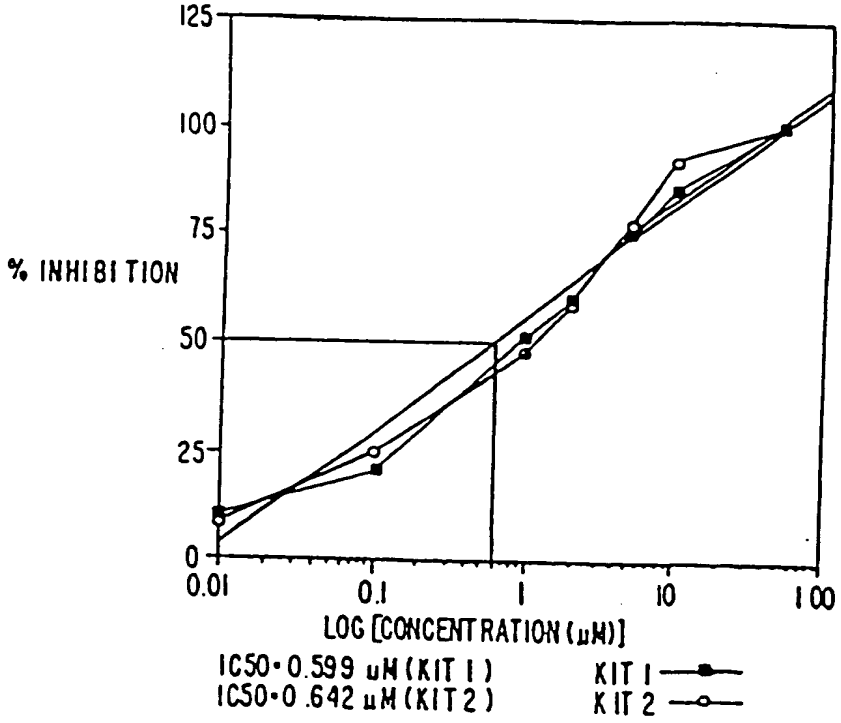


FIG.15B

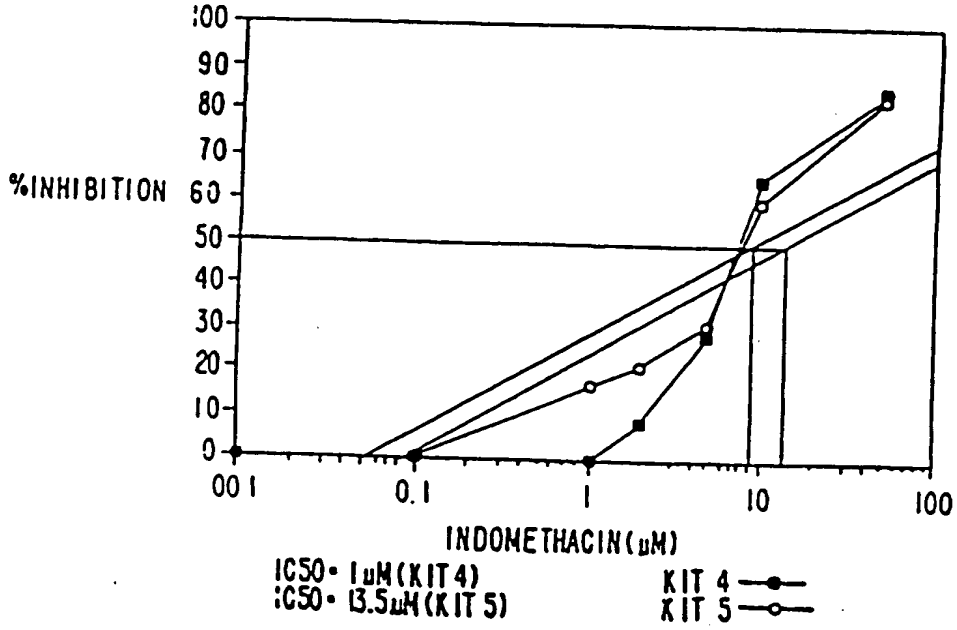
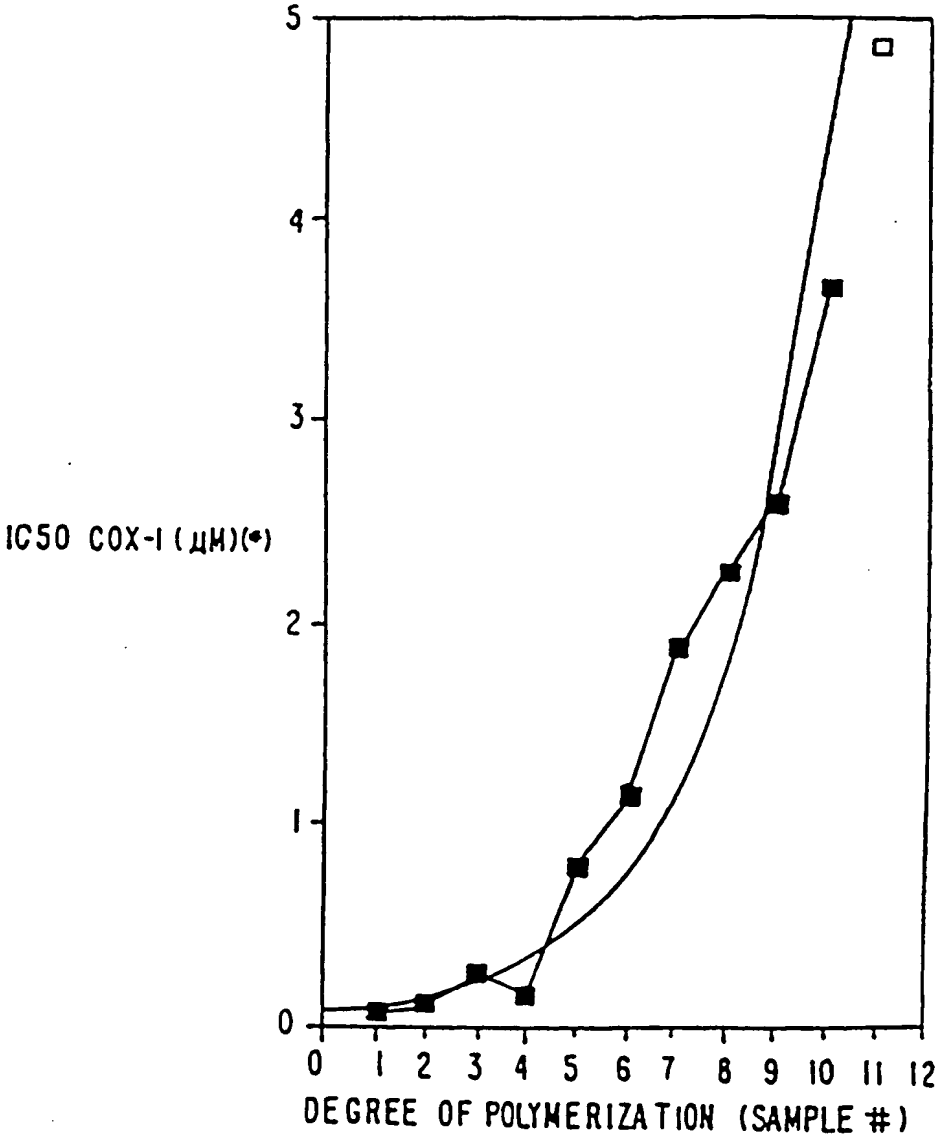
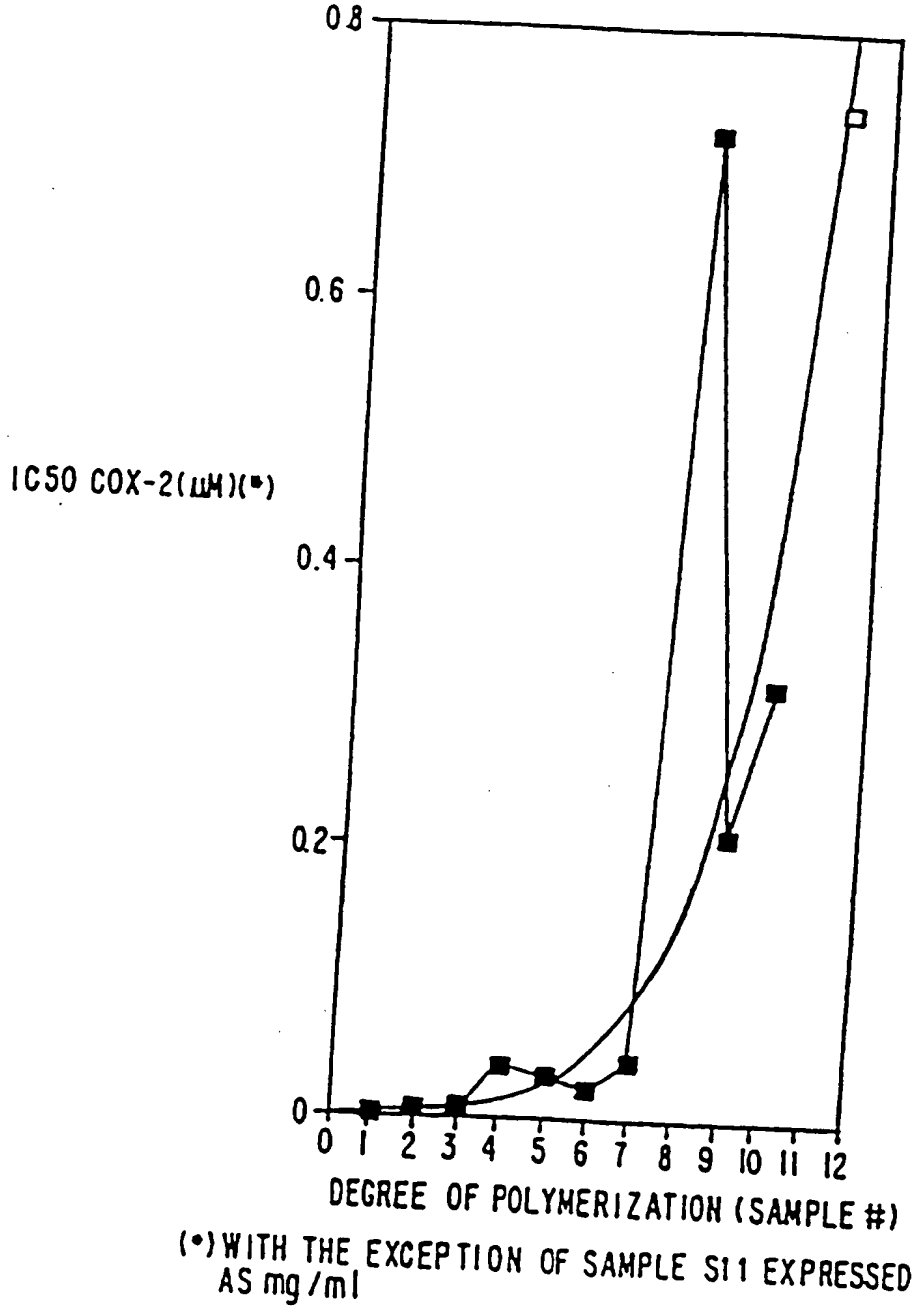


FIG.16A



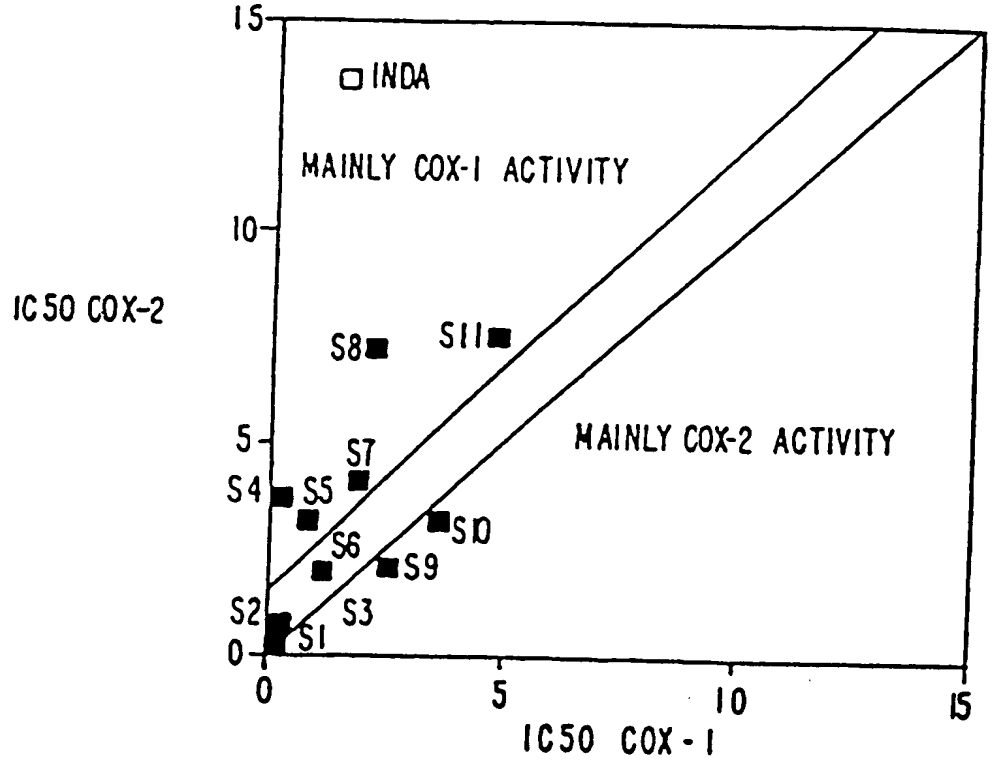
(*) WITH THE EXCEPTION OF SAMPLE S11 EXPRESSED AS mg/ml

FIG.16B



(*) WITH THE EXCEPTION OF SAMPLE S11 EXPRESSED AS mg/ml

FIG.17



(*) WITH THE EXEPTION OF SAMPLE S11

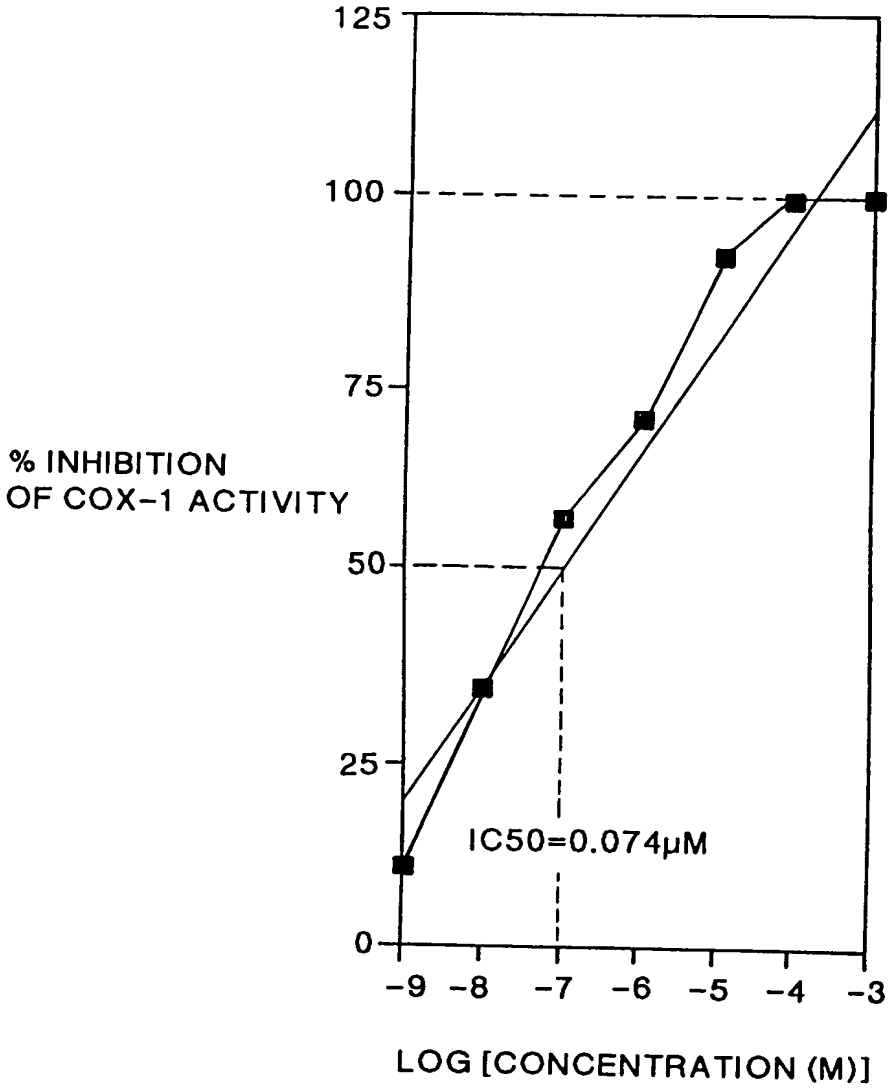


FIG.18A

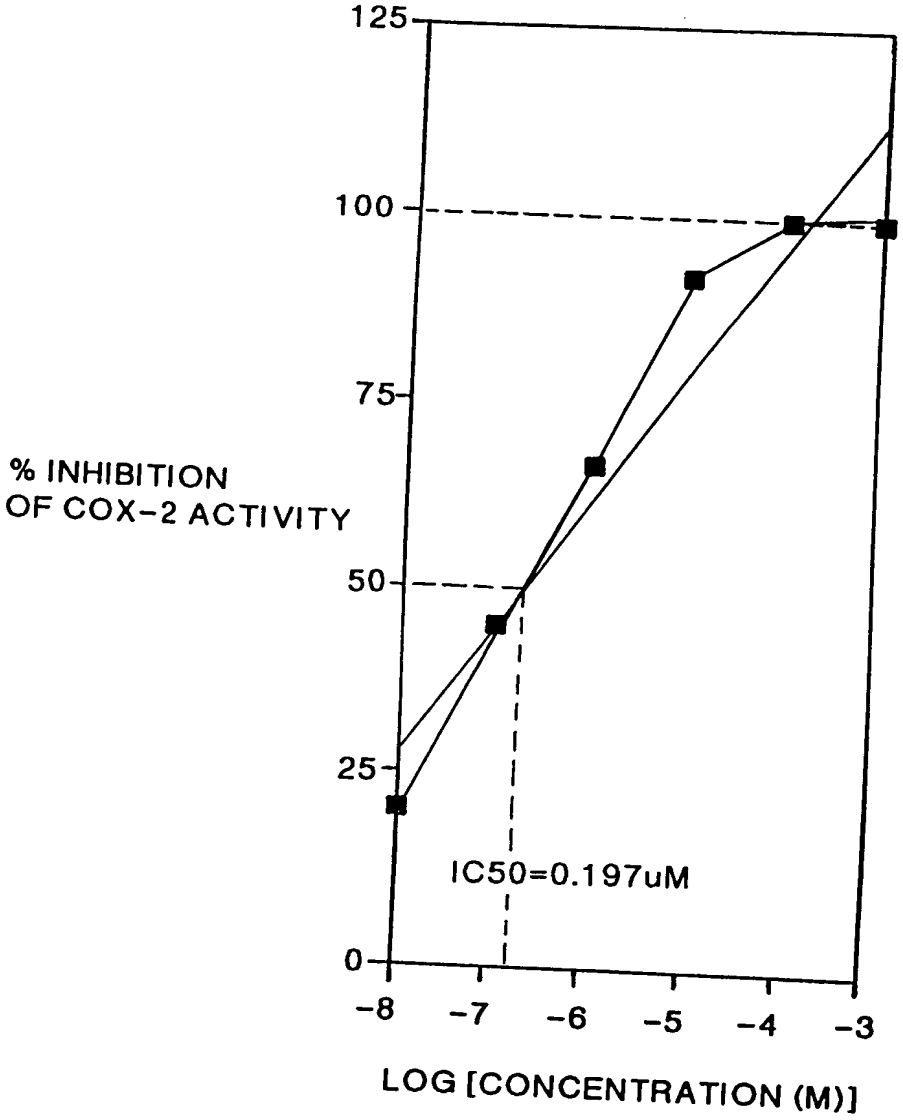


FIG.18B

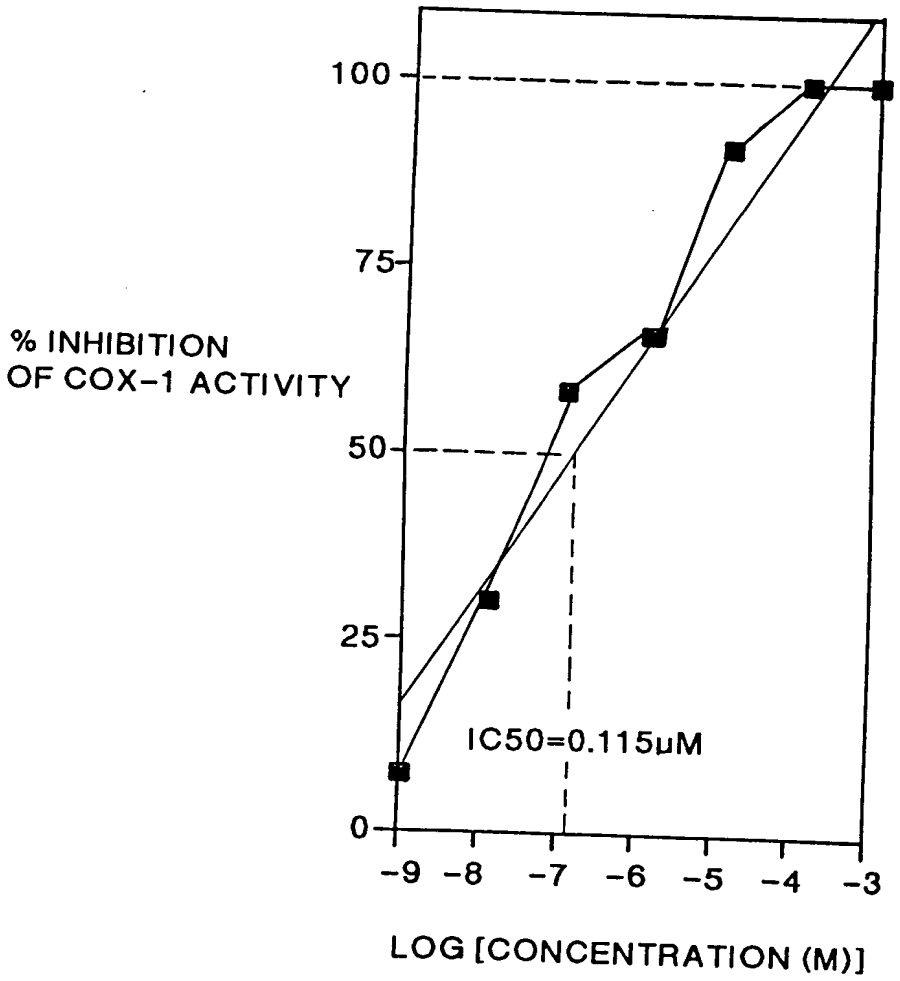


FIG.18C

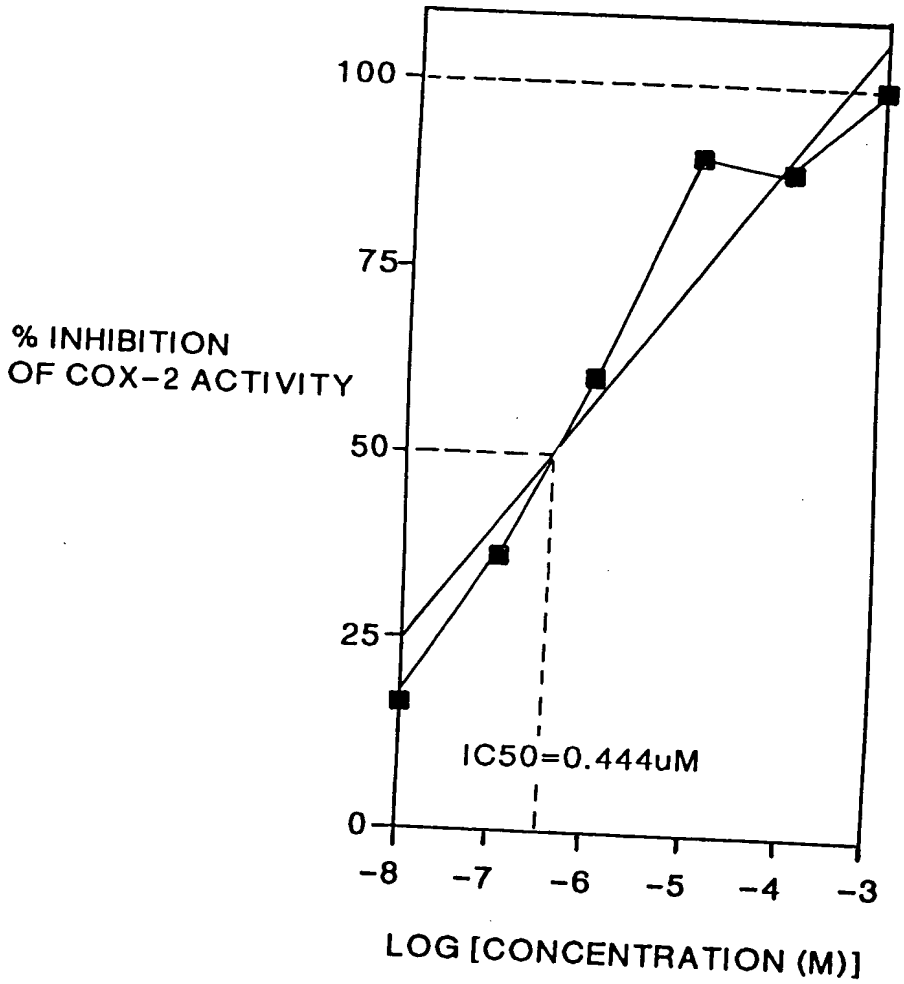


FIG.18D

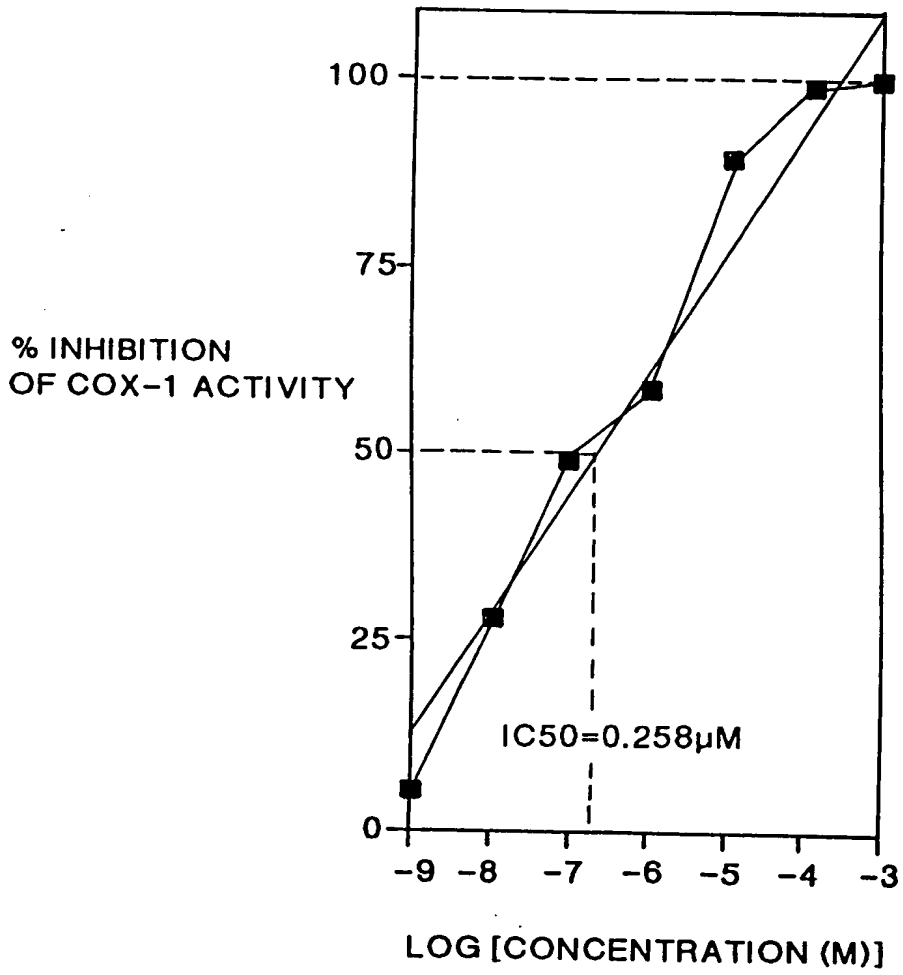


FIG.18E

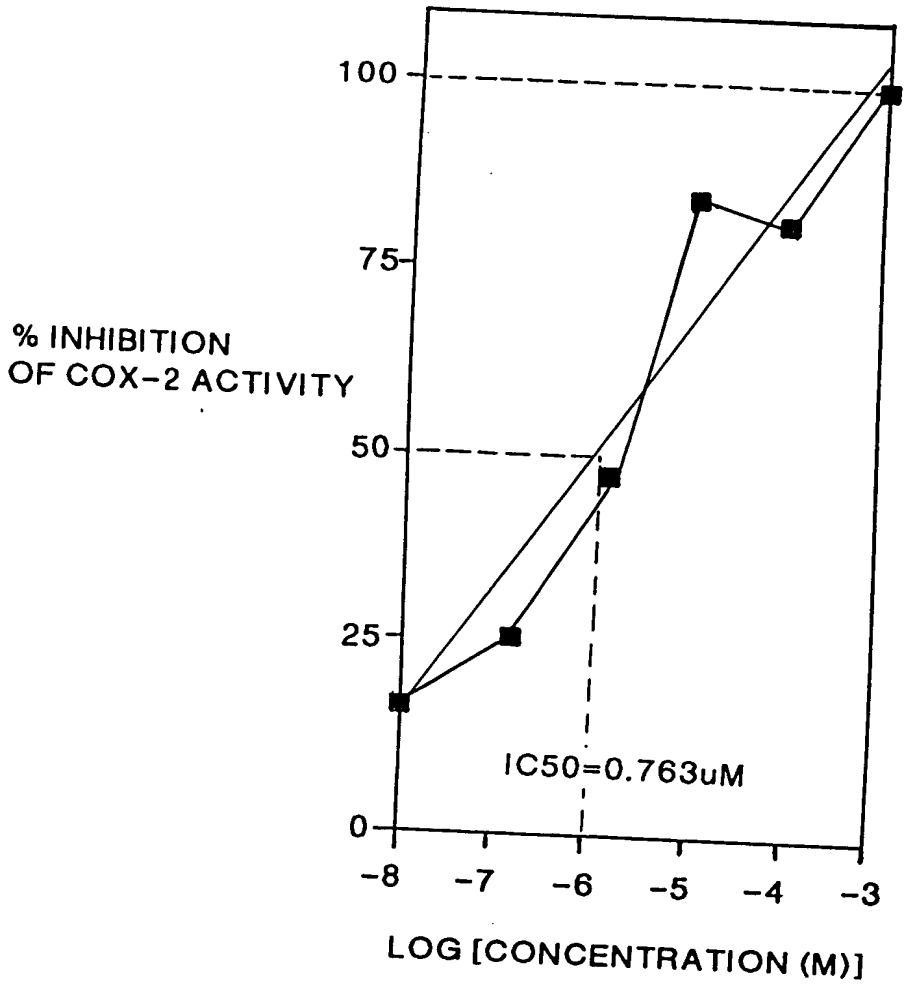


FIG.18F

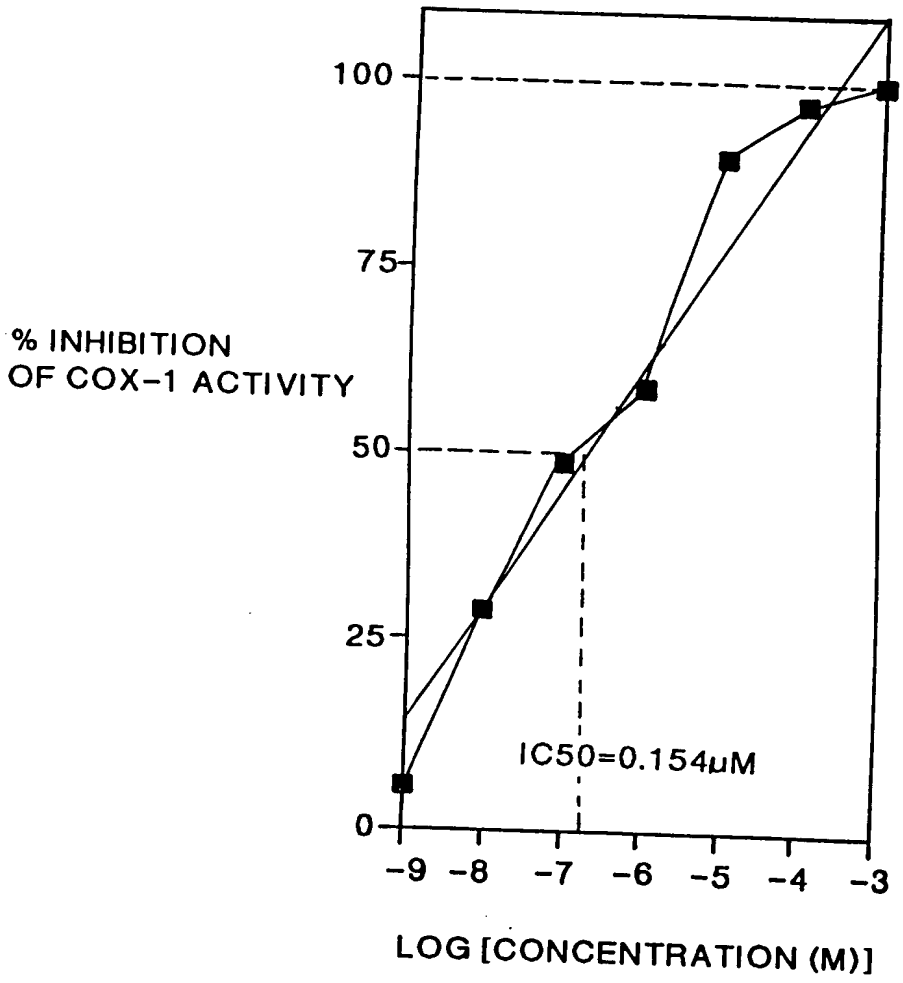


FIG.18G

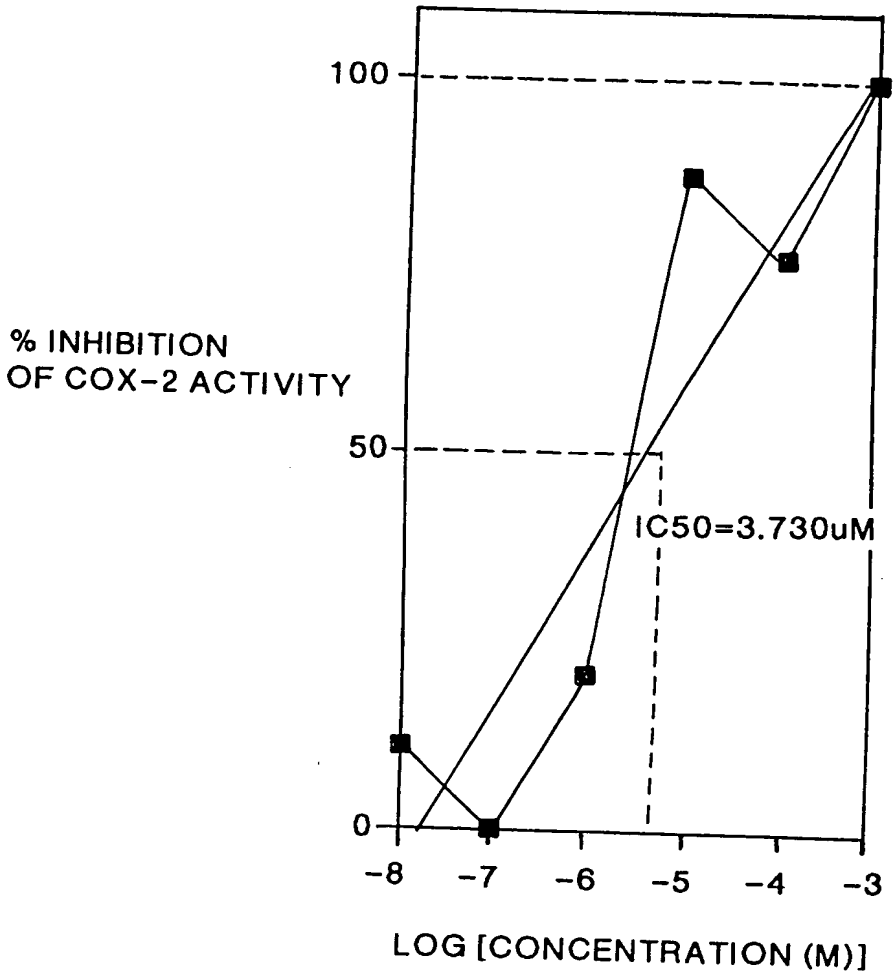


FIG.18H

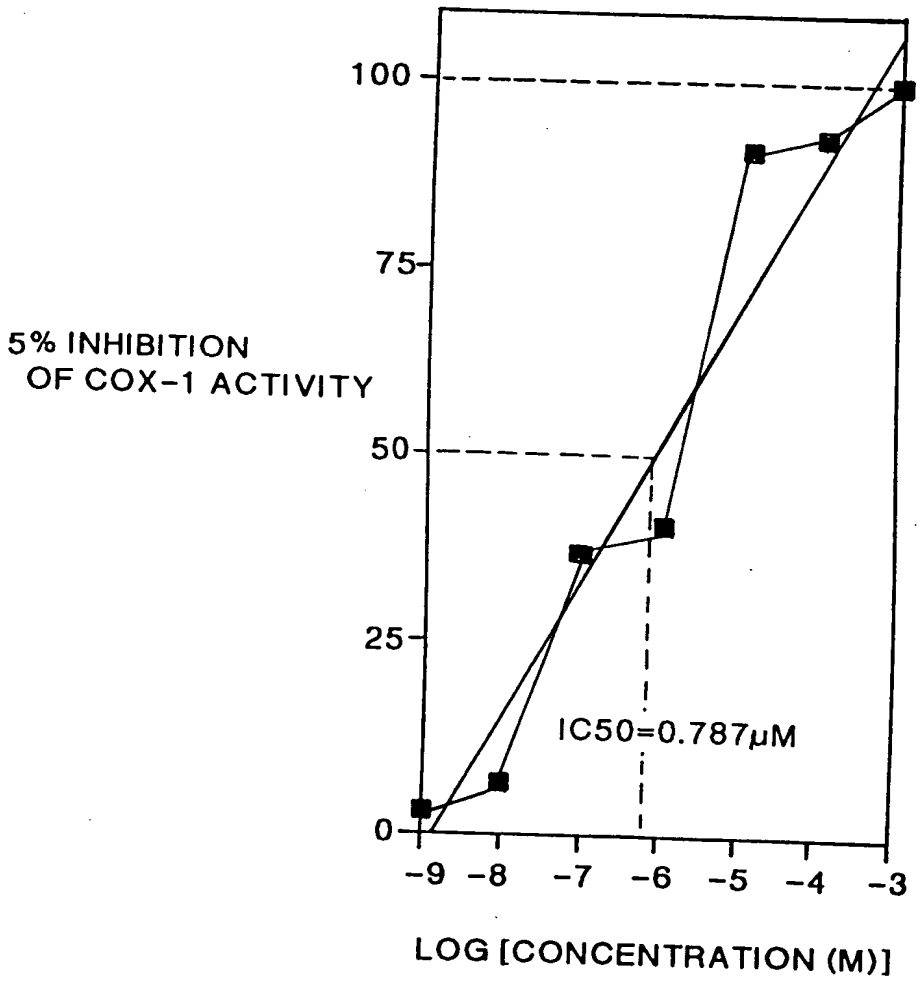


FIG.18 I

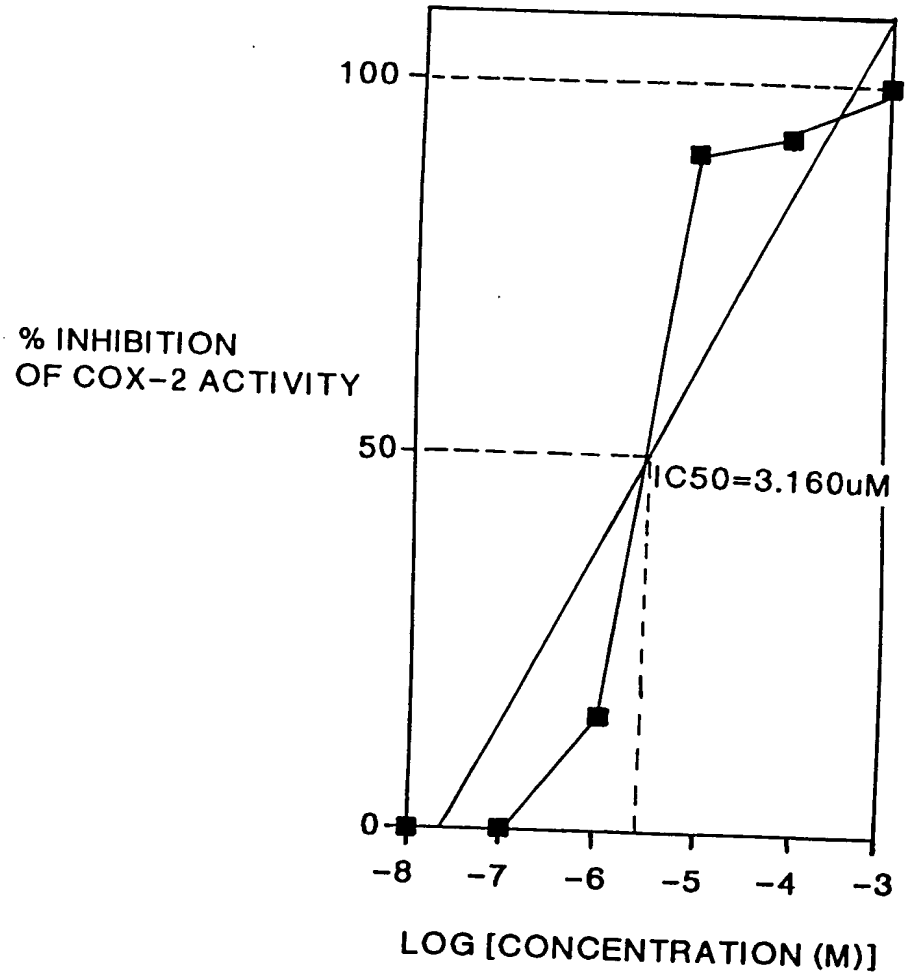


FIG.18J

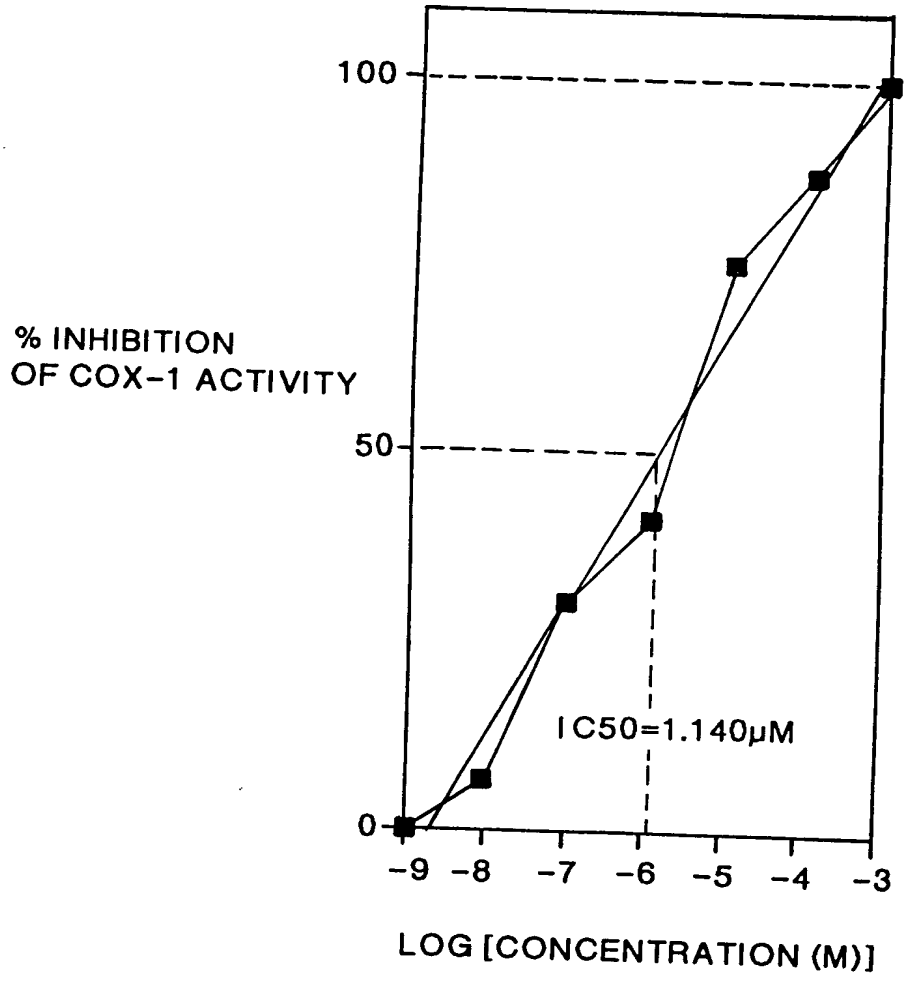


FIG.18K

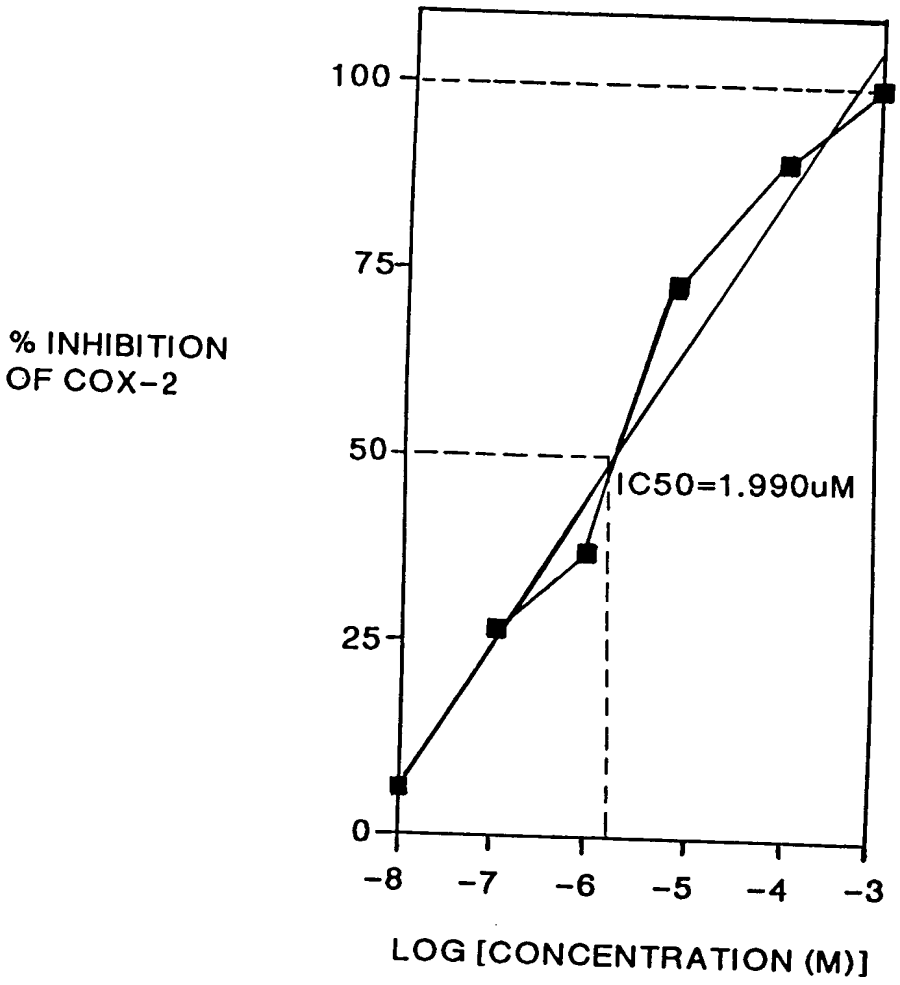


FIG.18L

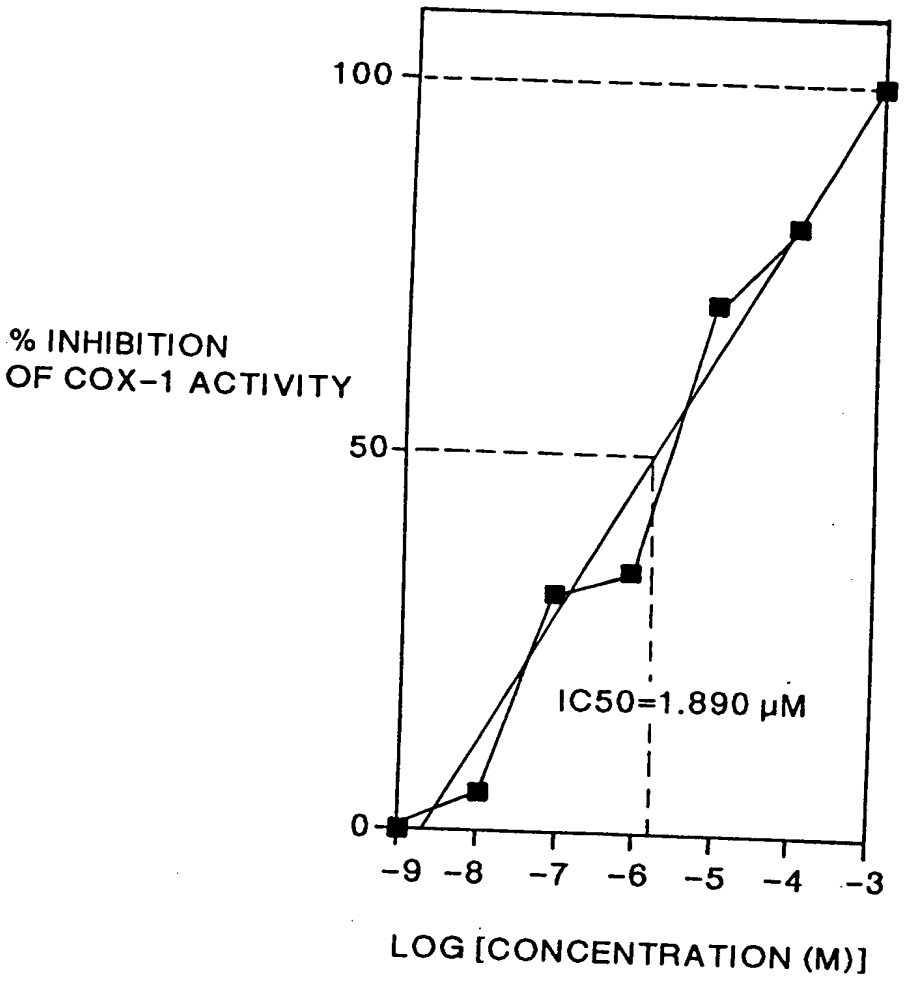


FIG.18M

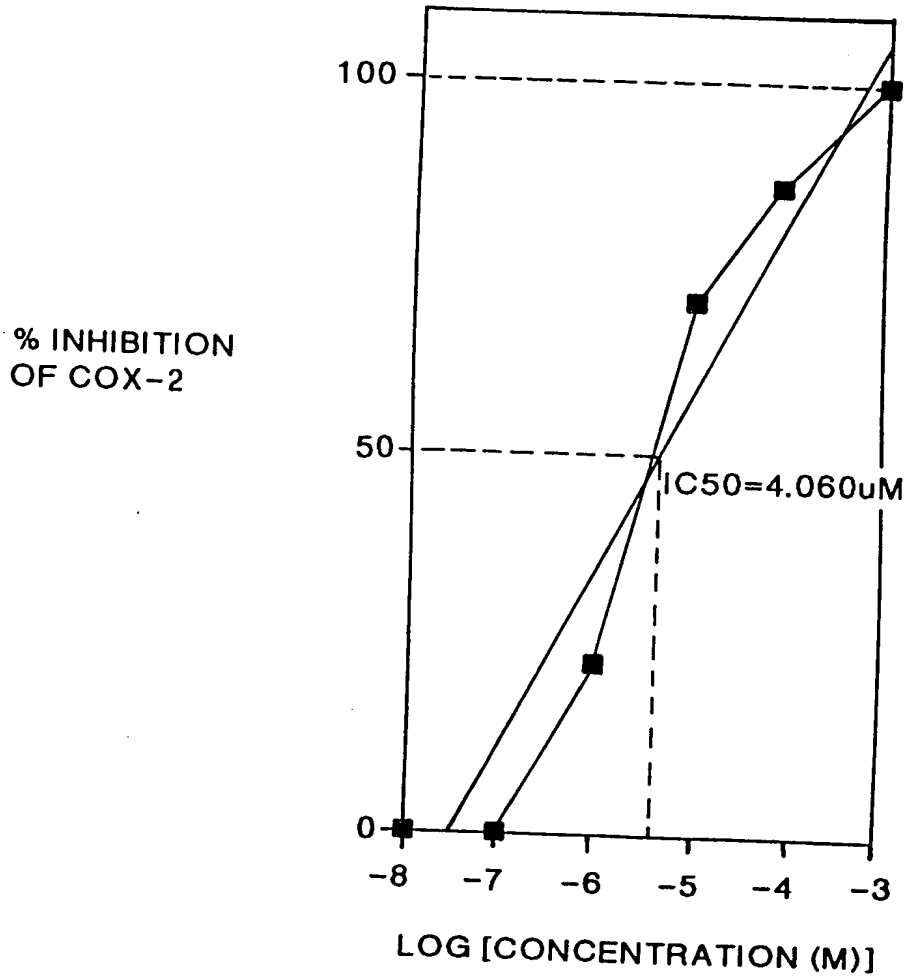


FIG.18N

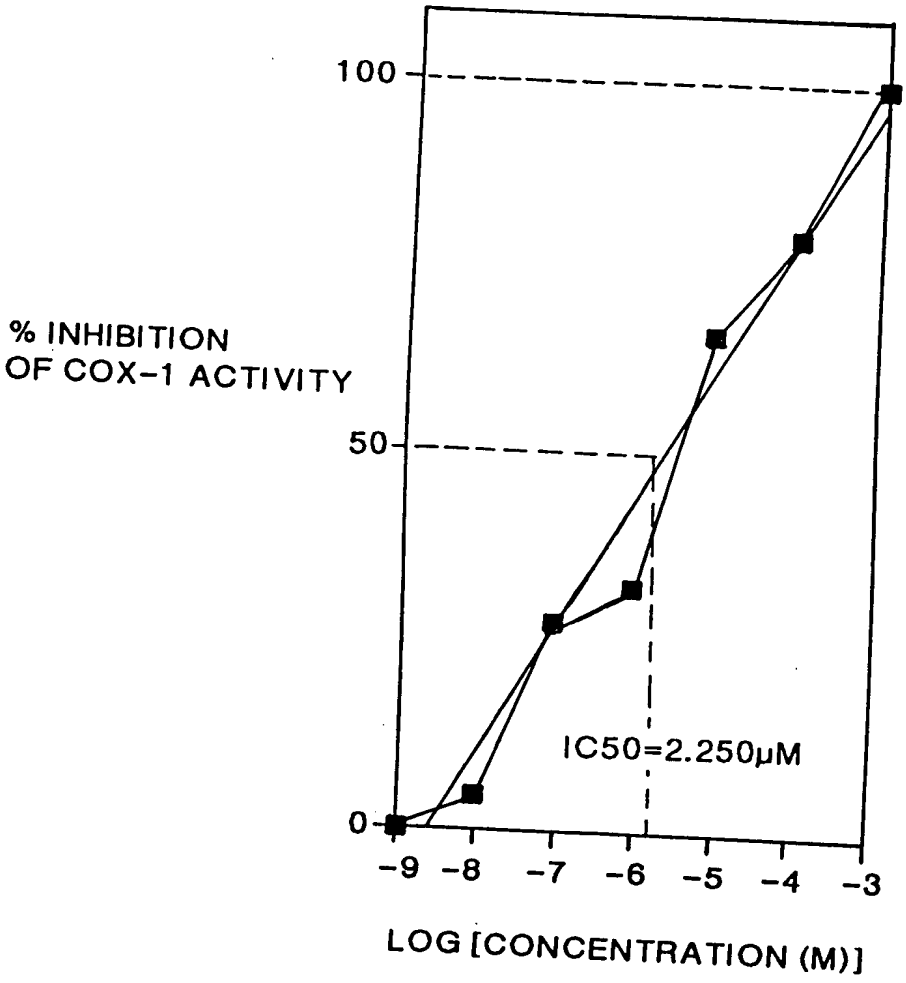


FIG.18O

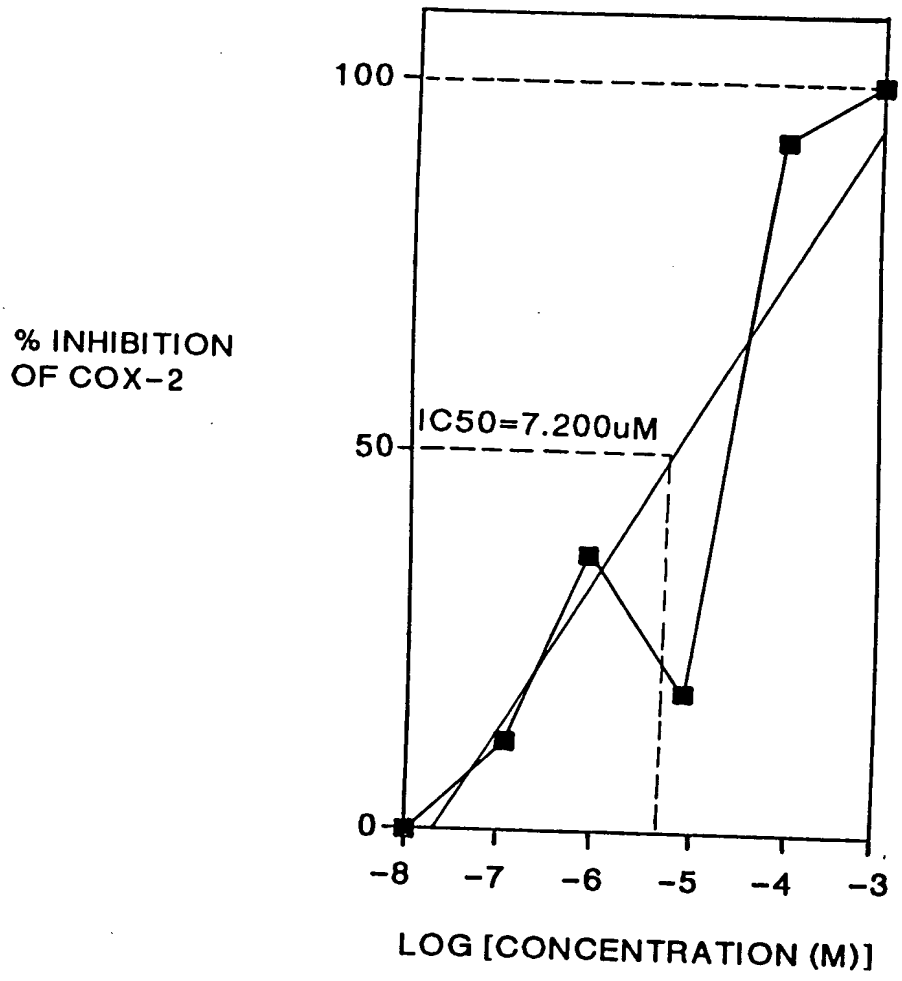


FIG.18P

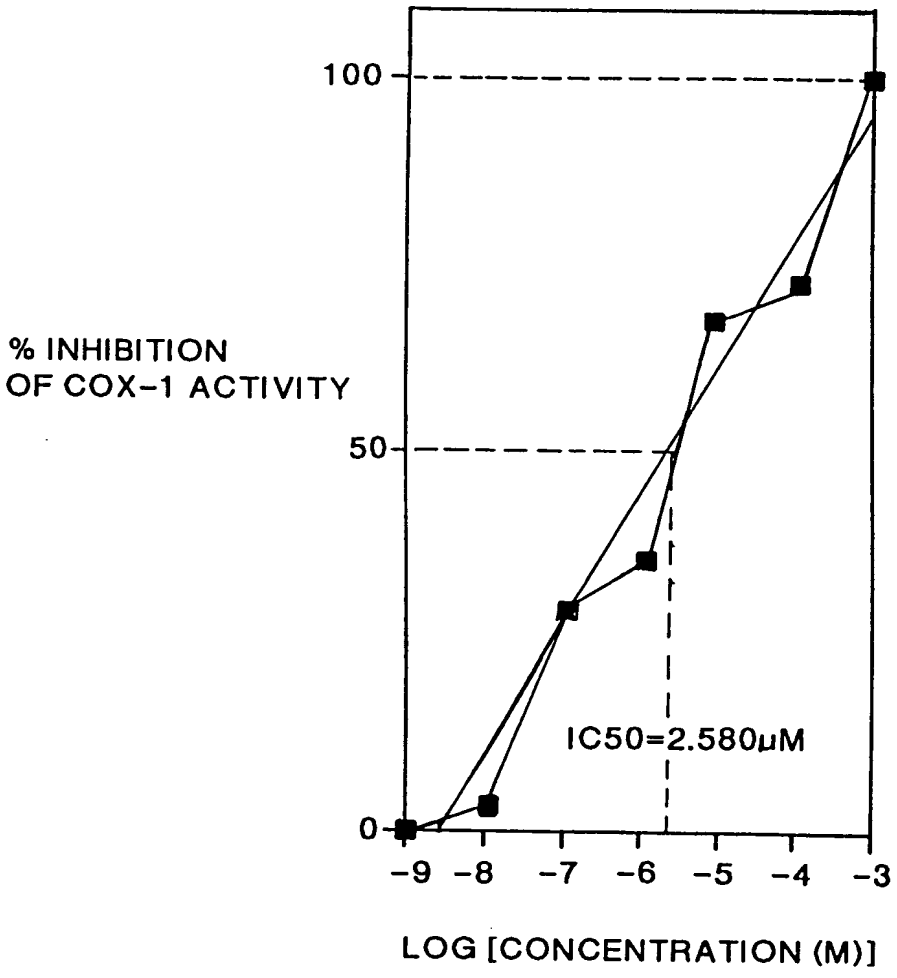


FIG.18Q

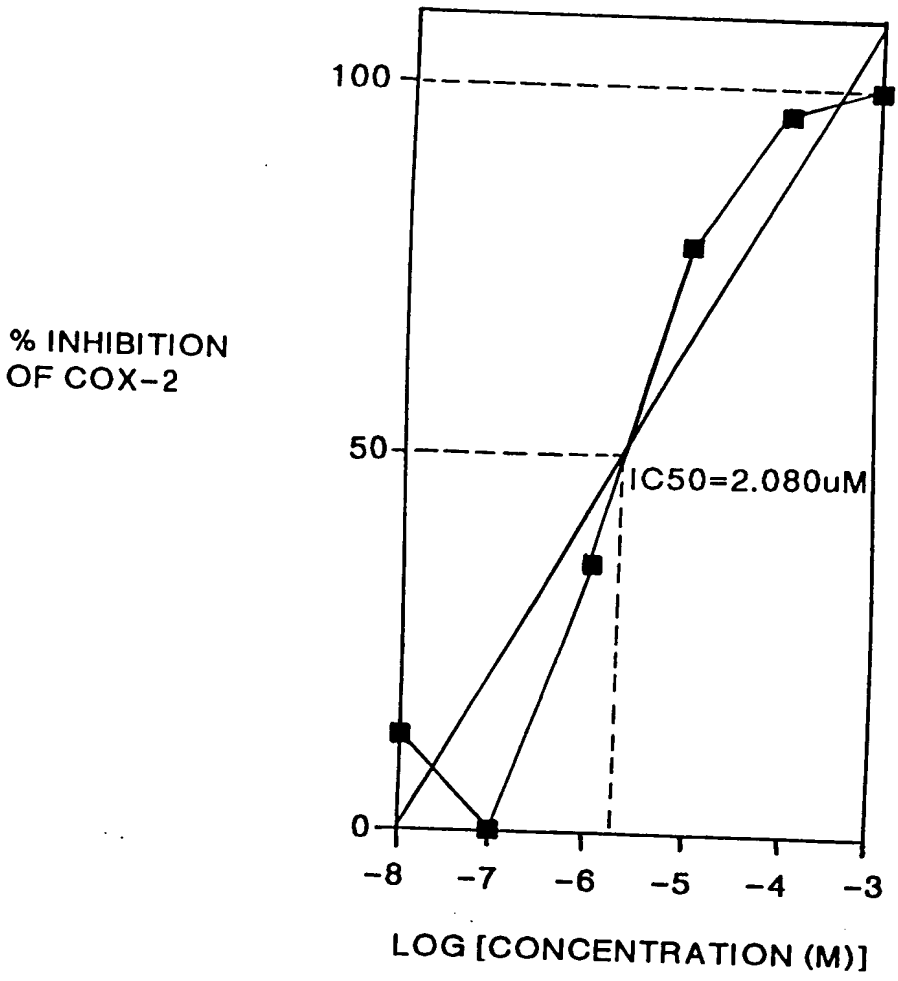


FIG.18R

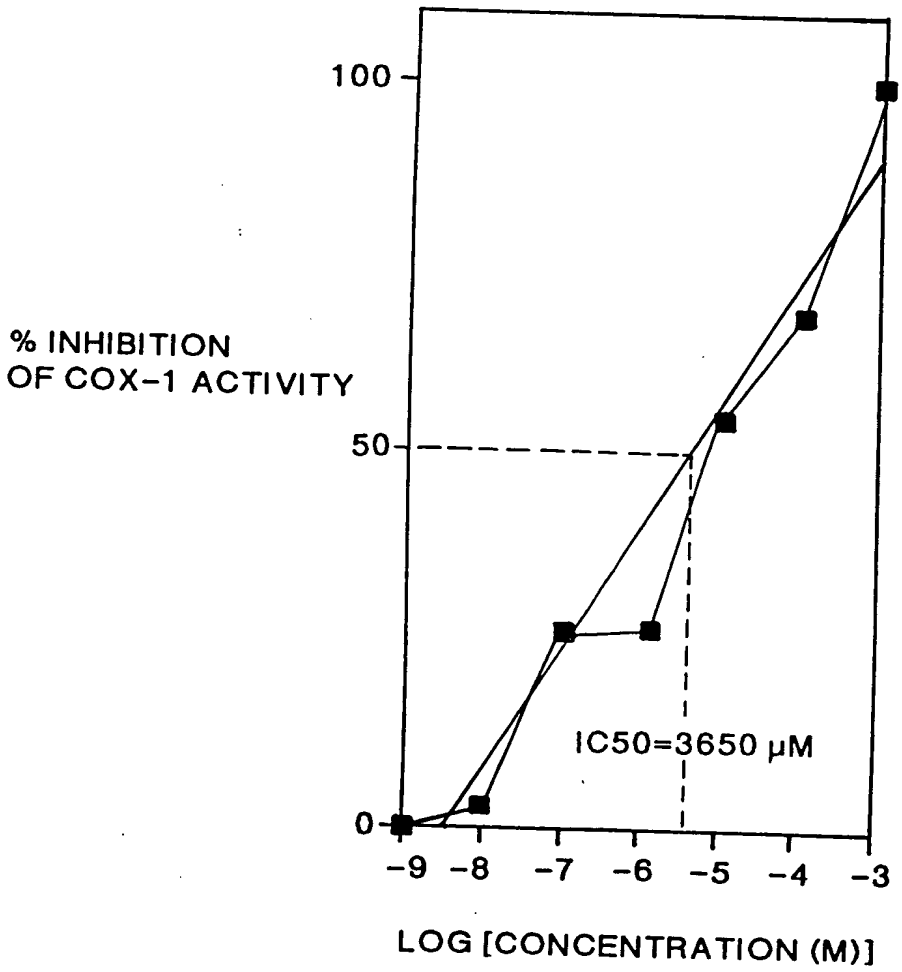


FIG.18S

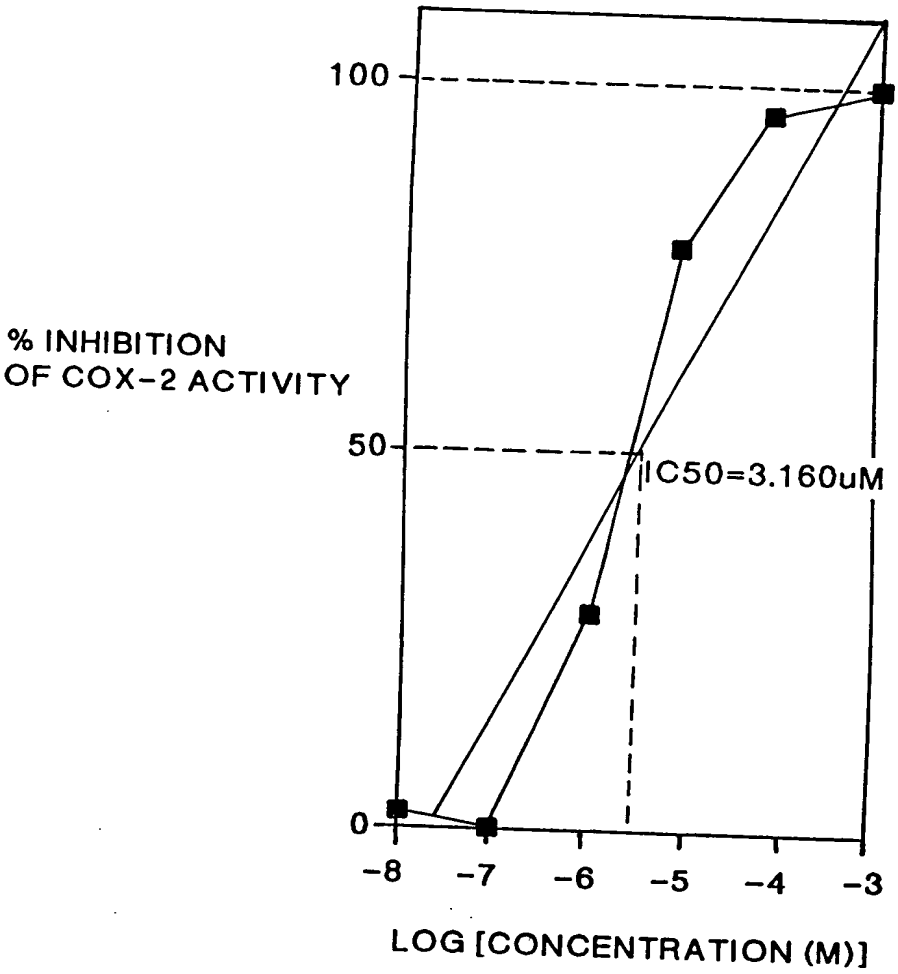


FIG.18T

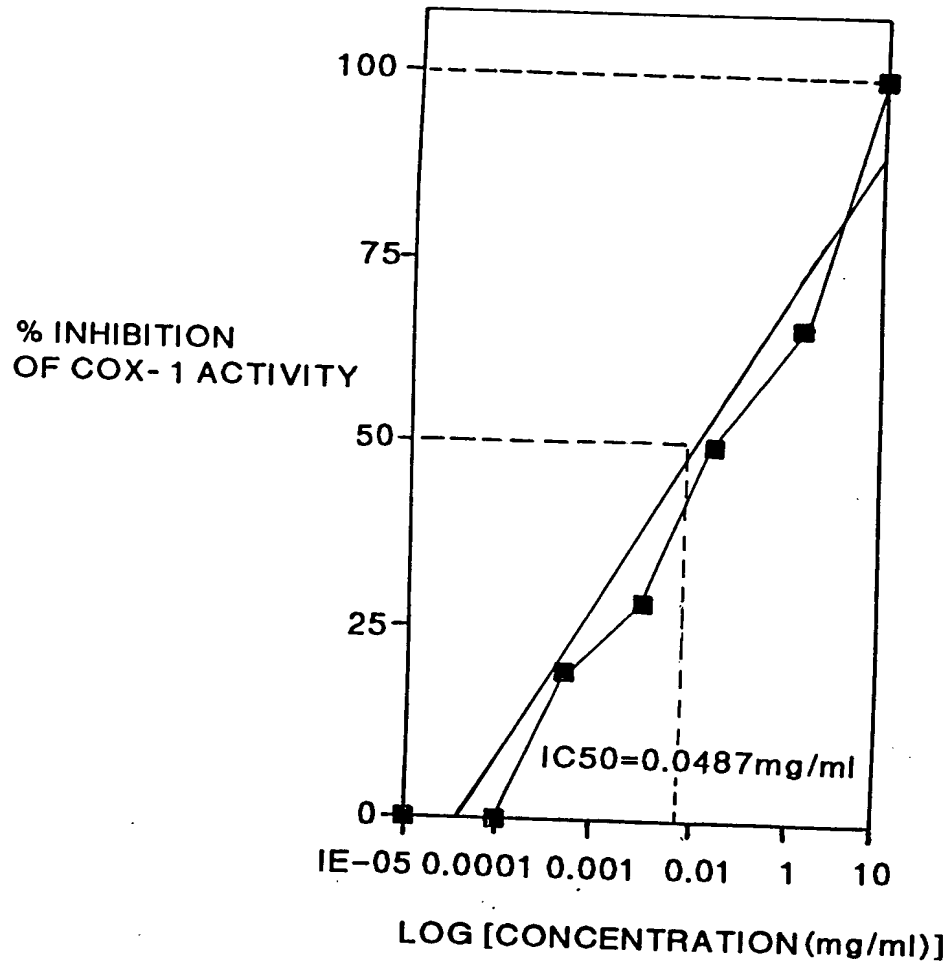


FIG.18U

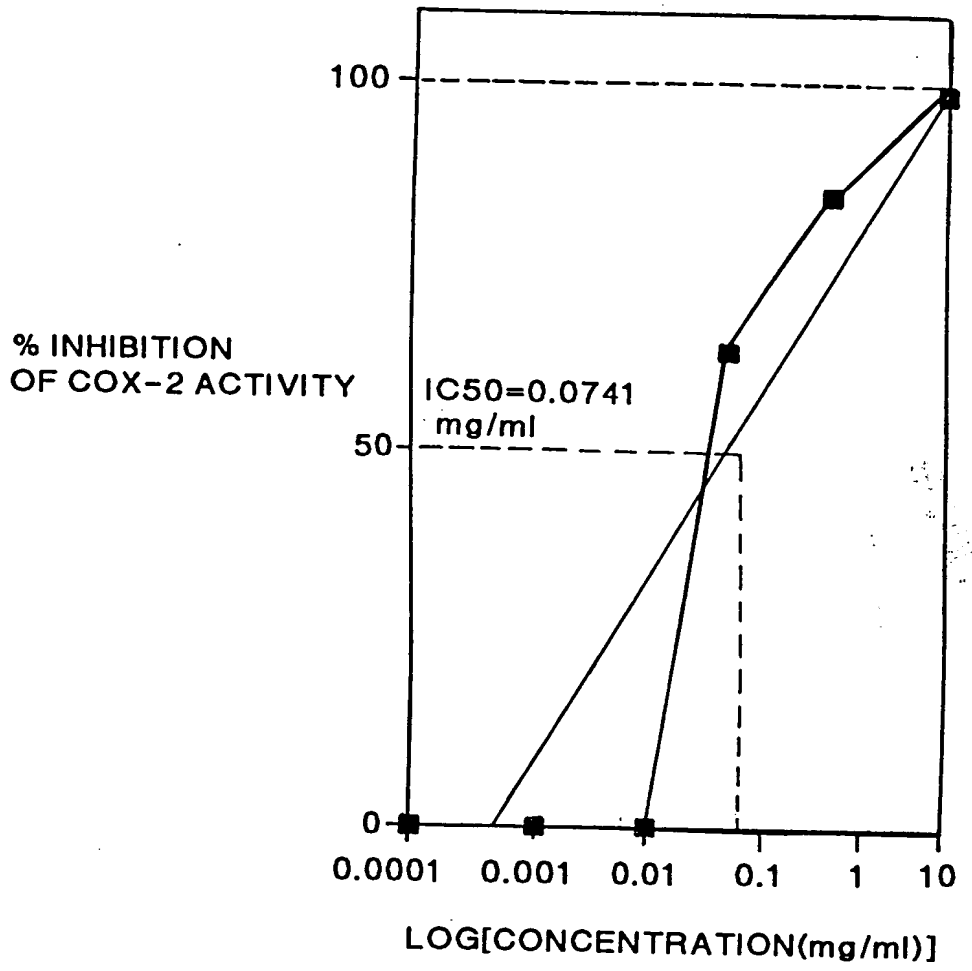


FIG.18V

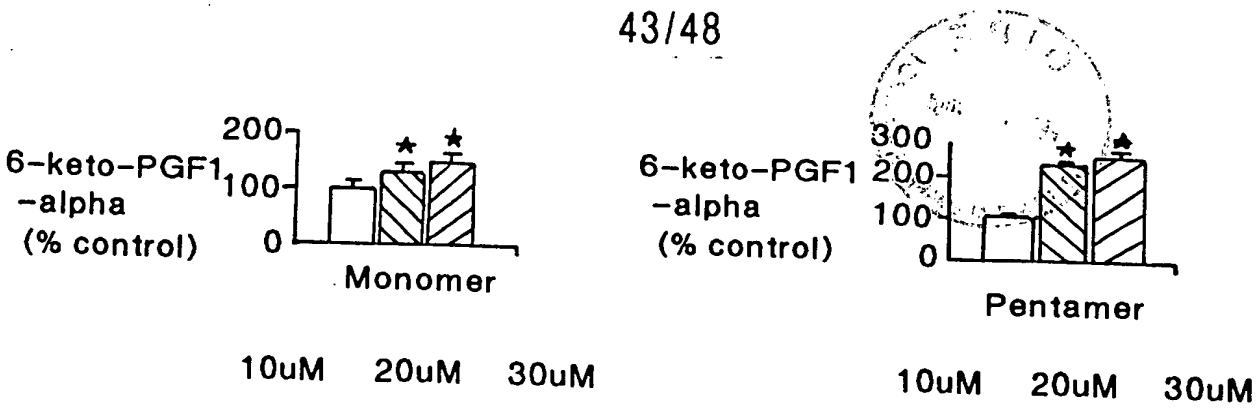


FIG.19A

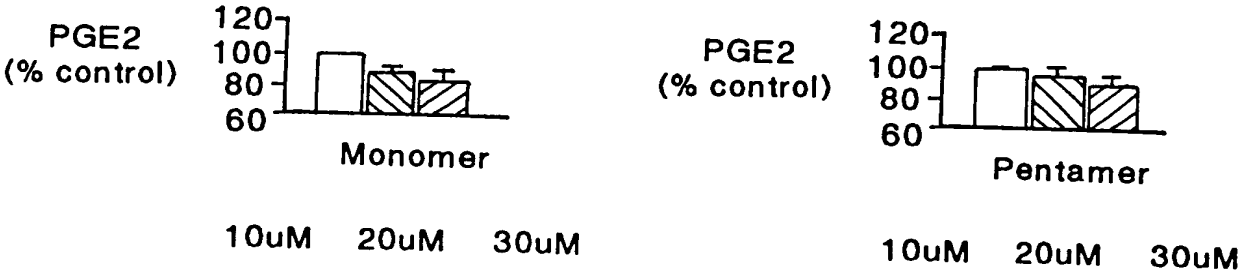


FIG.19B

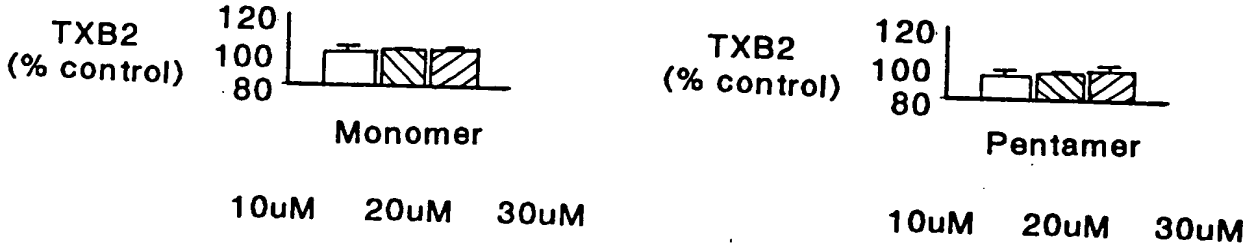


FIG.19C

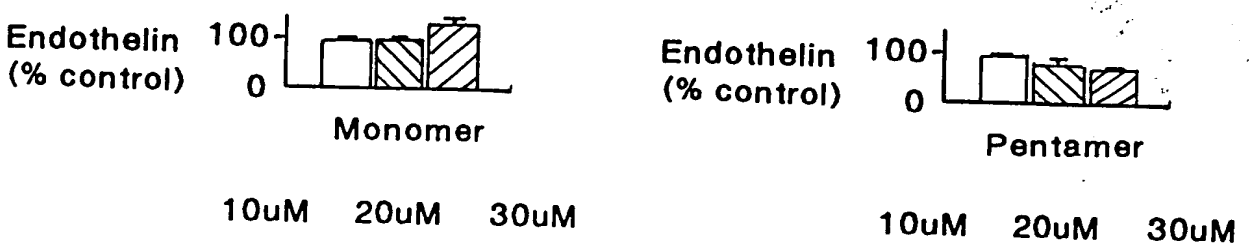


FIG.19D

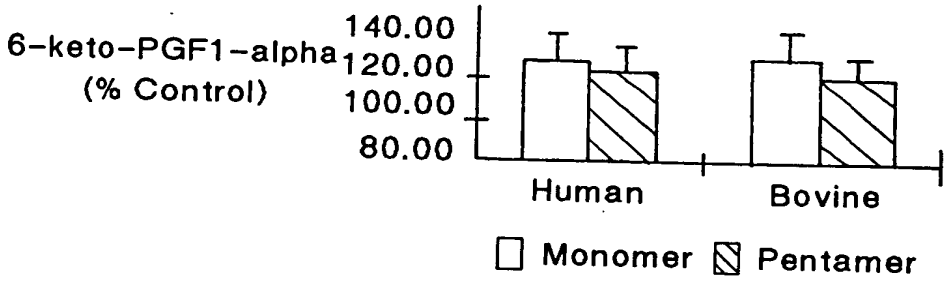


FIG.20A

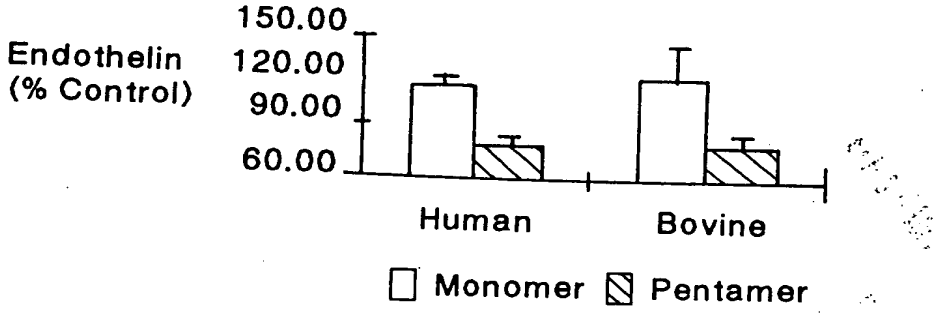
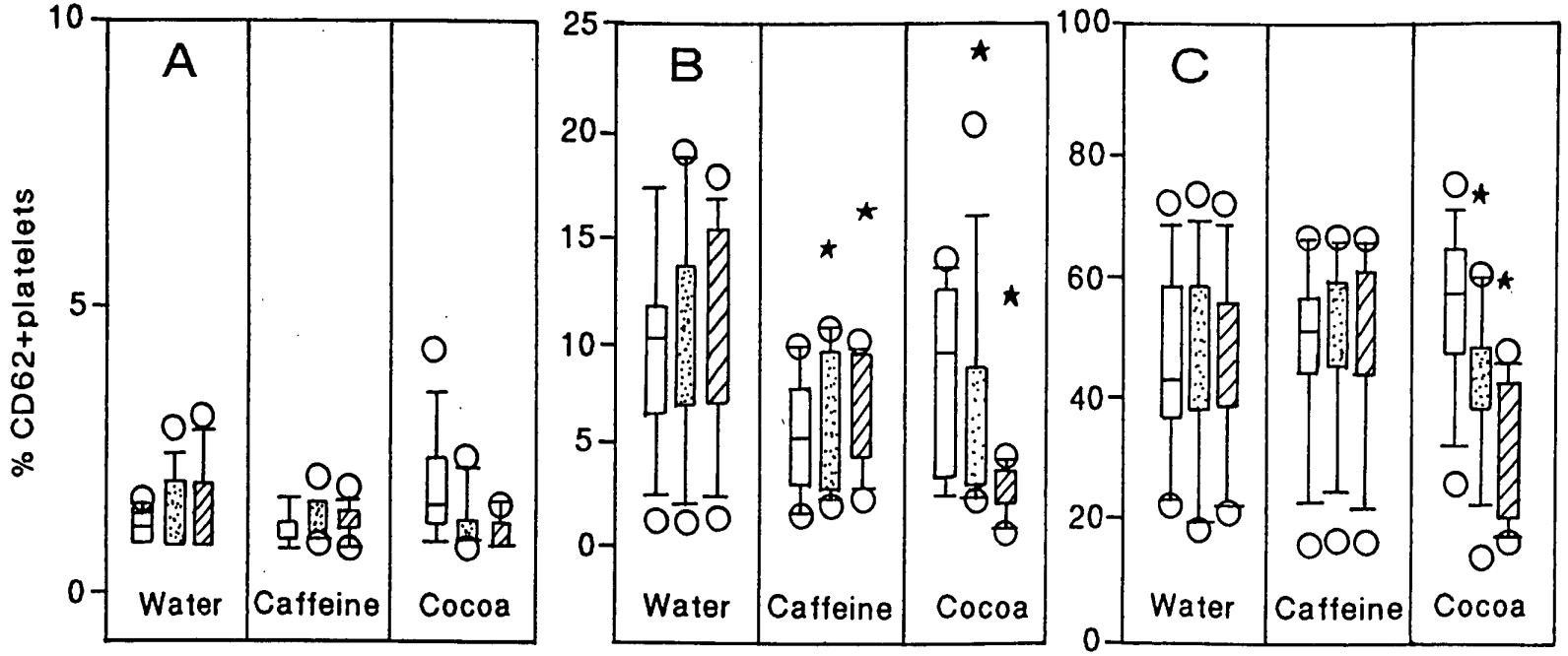


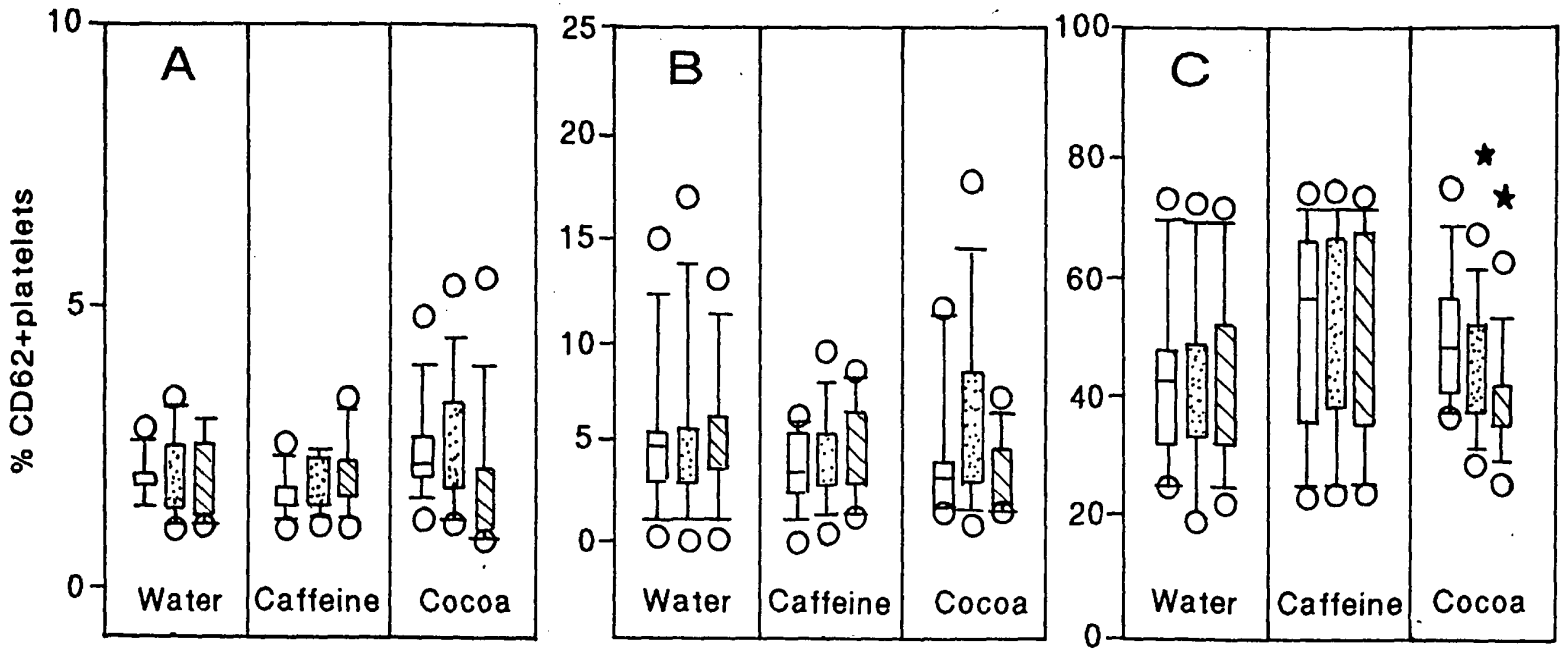
FIG.20B

FIG.21



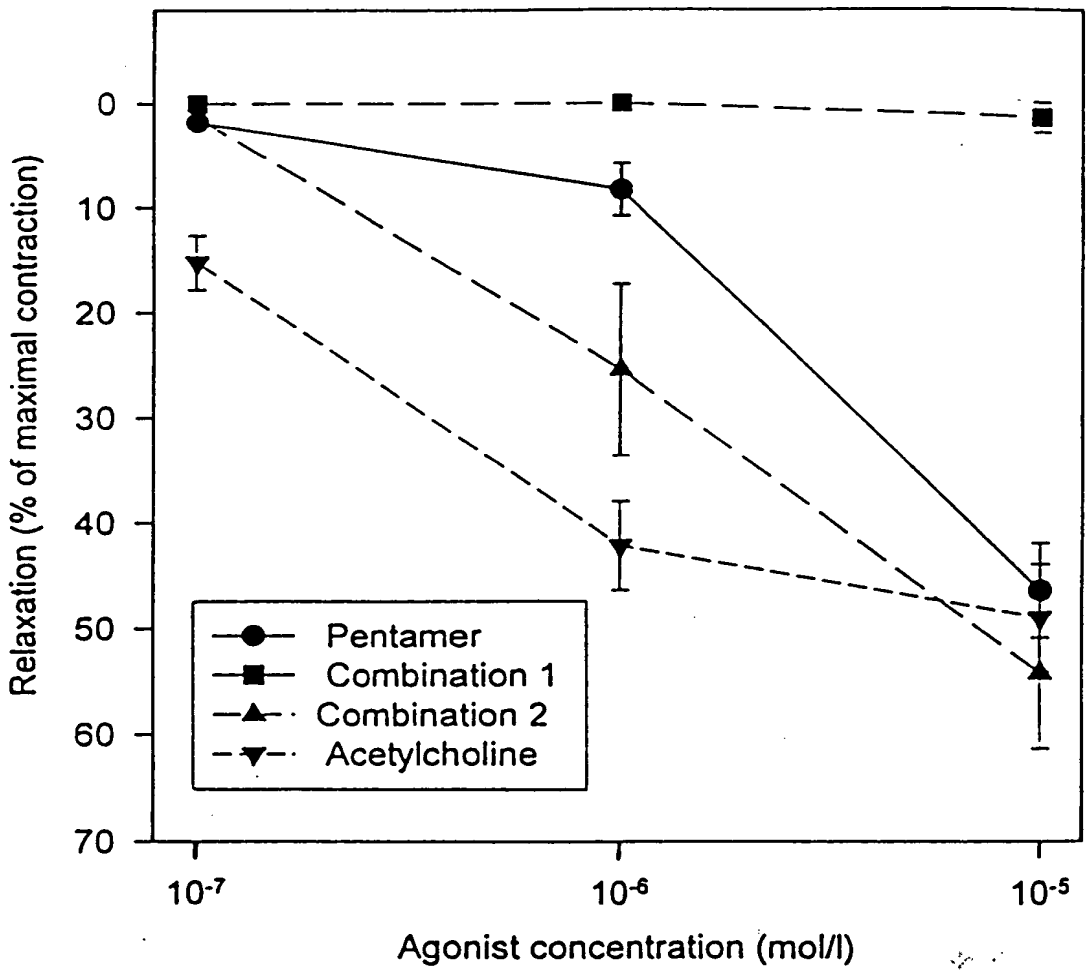
Effect of cocoa beverage consumption on platelet surface expression of activated GP11b-111a with and without simulation with weak agonisys. Platelet activation marker expression is presented as Tukey box plots at times zero (white boxes), 2 hours (light grey boxes), and 6 hours (dark grey boxes) post consumption of water, a caffeine-containing control beverage (caffeine) or a cocoa beverage (cocoa). (A) percentage of platelets expressing activated gp11b-111a (PAC1= platelets) without stimulation (B) after stimulation with epinephrine (20uM) or (C) with ADP (20uM). Activated GP11b-111a is expressed on the surface of activated platelets. Each box showsthe 25-75th percentile, the horizontal bar in the box shows the median. . The lines outside the box show the 10th and 90th percentile. Asterisks indicate P 0.05 betweenzero time and 6 hour hour time points of each respective data set repeated measure ANOVA on ranks, Student-Newman-Keuls multiple comparison method, n=10 in each

FIG.22



Effect of cocoa beverage consumption on platelet surfac surface expression of activated P-selection with and without stimulation with weak agonists. platelet activation marker expression presented as Tukey box plots at times zero (white boxes), 2 hours (light grey boxes) and 6 hours (dark grey boxes) post-consumption of water, a caffeine-containing control beverage (caffeine) or a cocoa beverage (cocoa).(A) Percentage of platelets expressing P-selection(CD62P+platelets) without stimulation, (P) after stimulation with epinephrine (20uM) or (C) with ADP(20uM). P-selection is expressed on the surface of activated Asterisks indicate $P<0.05$ between zero time and 2 hours and between zero time and six

FIG.23



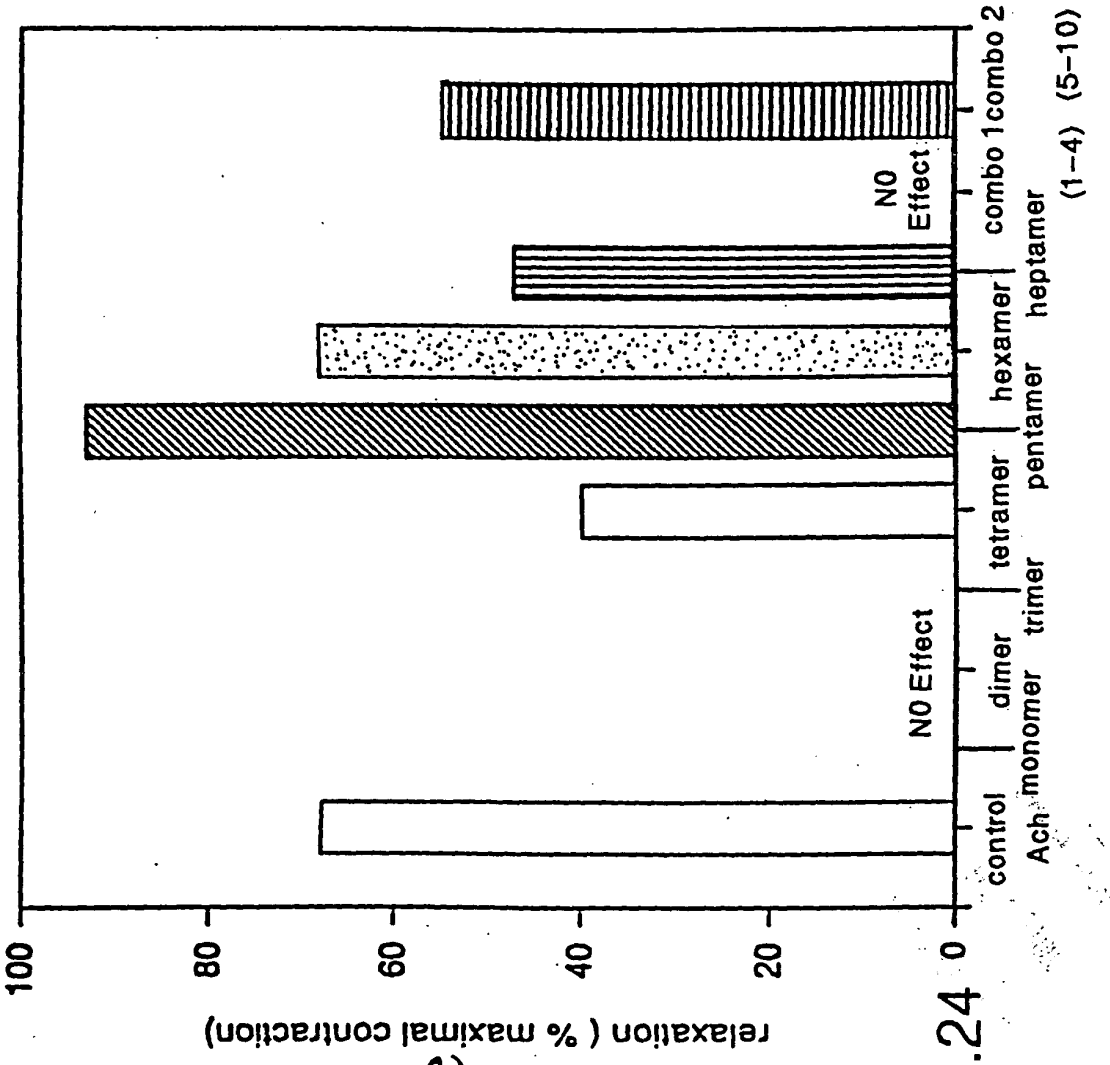


FIG.24

Single dose
10^{-5}M